Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé

Québec

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des technologies
et des modes
d'intervention en santé

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(CETS 99-4 RE)

ISSUES CONCERNING PRENATAL SCREENING AND DIAGNOSIS OF DOWN SYNDROME

Report submitted to

The Minister of Research, Science and Technology of Québec

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Conseil d'évaluation des technologies de la santé du Québec

MANDATE

To promote and support health technology assessment, disseminate the results of the assessments and encourage their use in decision making by all stakeholders involved in the diffusion of these technologies.

To advise the Minister on matters concerning the introduction, diffusion and use of health technologies and, to this end, give advice based on the assessment of their effectiveness, safety and cost, their impact on the healthcare system and their economic, ethical and social implications.

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Note : This information about the mandate and the Conseil's members reflects the situation when the French official report was published. On June 28, 2000, the name and the mandate were modified and new members were appointed.

ISSUES CONCERNING PRENATAL SCREENING AND DIAGNOSIS OF DOWN SYNDROME

Down syndrome (DS) is a common chromosomal abnormality, and the risk of giving birth to an affected child increases with maternal age. In Quebec, pregnant women aged 35 and over have had access to prenatal diagnosis for some years, using amniocentesis followed by karyotyping during the second trimester of pregnancy. However, this costly and invasive technique presents risks for both mother and fetus, and is therefore unsuitable for use in all pregnant women.

DS prenatal screening using maternal serum markers is now available. This avoids amniocentesis-related problems, while permitting estimation of a pregnant woman's individual risk of having a child with DS. If the risk is considered high, amniocentesis is used to confirm the diagnosis.

The *Conseil d'évaluation des technologies de la santé (CETS)* was given the mandate by the *Ministère de la Santé et des Services sociaux* to assess whether it would be appropriate to introduce prenatal screening using maternal serum markers in Quebec. The assessment presented in this report is based on a cost-effectiveness analysis, accompanied by a description of DS, a review of the literature on the effectiveness of screening and diagnostic techniques, a study of existing programs and a discussion of ethical issues.

In conclusion, *CETS* considers that DS screening using serum markers should be made available to all pregnant women in Quebec, regardless of their age. Their participation should be voluntary, and they should freely give their informed consent after receiving complete, high-quality information from the professionals involved. The best screening strategy is one that enables more cases of DS to be diagnosed with the lowest risk of iatrogenic fetal loss at an acceptable cost, and that respects existing rights with respect to amniocentesis as of age 35. It must also be readily adaptable to new technological developments.

In disseminating its opinion, *CETS* wishes to provide the best possible information to decision makers concerned with this problem at various levels within Quebec's system of health and social services.

Renaldo N. Battista
President

SUMMARY

INTRODUCTION

Down syndrome (DS) is a common chromosomal abnormality, and the risk of having an affected child increases with maternal age. In Quebec, pregnant women aged 35 and over at the time of delivery have had access to prenatal diagnosis for some years, using amniocentesis followed by karyotyping during the second trimester of pregnancy. However, this costly and invasive technique presents risks for both mother and fetus, and is therefore unsuitable for use in all pregnant women. DS prenatal screening using maternal serum markers is now available and is free of such drawbacks. It also enables estimation of a pregnant woman's individual risk of having a child with DS. If the risk is considered high, amniocentesis is used to confirm the diagnosis. Several Canadian provinces and a number of countries in the world already make prenatal screening with serum markers available.

The *Conseil d'évaluation des technologies de la santé (CETS)* was given the mandate by the *Ministère de la Santé et des Services sociaux* to assess whether it would be appropriate to introduce prenatal screening using maternal serum markers in Quebec. This report presents a description of DS, a review of the literature on the effectiveness of screening and diagnostic techniques, a description of programs already available in Canada and elsewhere, and a cost-effectiveness analysis on introducing maternal serum marker screening in Quebec. Particular attention has also been paid to ethical issues inherent to DS prenatal screening.

DESCRIPTION OF DOWN SYNDROME

DS is the most common severe chromosomal abnormality known, and its incidence in the population is one in every 700 to 1,000 births. It can be caused by an extra chromosome at pair 21, a translocation or a mosaicism. Clinical presentation varies, but the phenotype is characteristic and is always accompanied by a certain degree of mental retardation. The risk of giving birth to a child with DS increases with the mother's age, and rises much more rapidly after age 35. Using the expected birth distribution for Quebec in the year 2000 and the risk based on maternal age, up to 111 cases of DS can be expected for that year.

DOWN SYNDROME PRENATAL SCREENING AND DIAGNOSIS

Prenatal screening covers the procedures available to all pregnant women in order to identify those at high risk of having a DS child. Risk is considered high when it exceeds a selected cutoff point, generally between 1:250 and 1:384. Screening can be carried out using serum markers or ultrasound, but new techniques are currently under development. The goal of prenatal diagnosis is to determine whether the fetus is, in fact, affected when screening has indicated a high-risk pregnancy. Amniocentesis and chorionic villus sampling are the diagnostic methods most commonly used.

Serum marker screening

Serum marker screening consists of measuring levels of specific markers in the maternal blood. The most often used markers are AFP, hCG and unconjugated estriol. Measurements are made during the second trimester, between the 15th and 18th week of gestation. The three markers are combined to form a "triple marker" test. However, other markers are also available, increasing the number of possible combinations. Serum markers are generally considered to provide a detection level of 65%, with a false positive rate of 8%. The detection rate represents the proportion of DS cases expected at birth that were detected by the test. The false positive rate represents the proportion of unaffected pregnancies for

which screening indicated an elevated risk of DS. While ultrasound is used in combination with the markers to confirm gestational age, it can also be used as a screening technique.

Some markers can be used during the first trimester of pregnancy. Although they render earlier diagnosis possible, their use is still not very widespread. New techniques are now being studied – the most promising are based on markers such as inhibin A or PAPP-A – but these must be validated before their use can be recommended.

Prenatal diagnosis

The prenatal diagnosis of DS is carried out by analyzing the karyotype of fetal cells obtained by amniocentesis or chorionic villus sampling. Amniocentesis can be performed during the first or second trimester, but presents greater risk for both mother and child in the former. It is therefore usually performed during the second trimester, and permits diagnosis of other chromosomal abnormalities. Sensitivity and specificity are near 100%. While the maternal risks associated with the procedure are small, it can cause iatrogenic fetal loss in 0.5 of cases, based on Quebec estimates.

The use of chorionic villus sampling is very limited in Quebec. This technique can be performed during the first trimester of pregnancy, but presents a greater risk of fetal loss and a higher rate of false positive and false negative results, in addition to being associated with an increase in fetal limb malformation. New diagnostic techniques are being developed, notably the identification of fetal cells in maternal blood.

The importance of genetic counselling

DS screening is based on the concept of risk, by permitting estimation of a pregnant woman's risk of giving birth to an affected child. Its major drawback, however, is that it generates a high number of false positive results. This means that women with an unaffected pregnancy but whose test results indicate they are at high risk are counselled to have amniocentesis, with the associated risk of iatrogenic fetal loss. It should be noted that DS screening and diagnosis take place during the second trimester of pregnancy and that, after screening, the mother and/or couple have limited time to make important decisions. If they agree to prenatal screening, they must receive all the necessary information so that they can understand the implications and make an informed choice. Genetic counselling is therefore indispensable if the nature and impact of the two risks involved are to be fully understood.

Current status of screening and diagnostic programs

In 1985, Manitoba became the first Canadian province to provide a provincial prenatal screening program using a single marker, AFP. Ontario followed in 1993 with a similar program that was based on the triple marker. In France, serum screening has been available at the national level for some years. Other European countries and the United States also offer such programs, although their modalities vary from country to country.

ETHICAL ISSUES

Prenatal screening and diagnosis raise a number of ethical questions for pregnant women and couples, health care professionals, society and government. DS screening and diagnosis offer no therapeutic solution, and the only preventive action possible is termination of the pregnancy. In view of this, voluntary participation of women and couples in DS screening is essential, and they must be able to count on objective, non-directing genetic counselling of high quality. Prenatal screening and diagnosis also raise other ethical issues, particularly with respect to the debate on selective birth. This debate is even more intense in the case of DS, since prenatal diagnosis pro-

vides no information on the degree of mental handicap nor the presence or absence of severe malformation. An additional consideration is the iatrogenic loss of unaffected fetuses. Finally, prenatal screening could lead to the reallocation of resources, which might result in fewer services being available to take care of affected individuals or provide support for their families.

SCREENING AND DIAGNOSTIC STRATEGY

This study analyzes various approaches to DS screening and diagnosis, which can be summarized as follows:

1) Amniocentesis, if 35 years and over at time of delivery (current situation in Quebec);
2) Universal maternal serum screening (MSS); amniocentesis if at high risk following serum test;
3) MSS if under 35, MSS or amniocentesis if 35 and over (current situation in Ontario);
4) MSS if under 35; amniocentesis if 35 and over;
5) MSS if under 37; MSS or amniocentesis if 37 and over;
6) MSS if under 37; amniocentesis if 37 and over.

The analysis in this report is performed from a public health perspective, the principal evaluation criterion being the cost-effectiveness ratio of the proposed approaches. The cost-effectiveness ratio is based on the cost per case diagnosed. We also considered the number of amniocenteses performed per case diagnosed and iatrogenic fetal loss per case diagnosed. Lastly, the analysis is based on the expected birth distribution for Quebec in 2000, actual and estimated costs of the various techniques in Quebec, effectiveness parameters reported in the literature, and current experience in Canada and elsewhere.

Cost-effectiveness analysis of the proposed approaches

The results suggest that the present program, which makes amniocentesis available to pregnant women aged 35 and over at time of delivery (strategy #1) is relatively expensive and ineffective. It would enable diagnosis of 28 cases of DS (out of 111 expected) at a total cost of $2.7 million and a C/E ratio of $97,965 per case. One hundred and ninety-seven amniocenteses would have to be performed for each case of DS diagnosed, and there would be 27 cases of iatrogenic fetal loss (ratio of iatrogenic fetal loss to cases diagnosed = 0.98). All of the other approaches considered appear to be more effective, with detection of 34 to 59 of the 111 cases of DS expected, a lower rate of iatrogenic fetal loss per case diagnosed and a lower C/E ratio (except in one instance, where the ratio is $112,544).

Strategy #2 (universal MSS; amniocentesis if at high risk) is attractive from the point of view of effectiveness with an acceptable C/E ratio, but would involve the loss of a current right – i.e. access to amniocentesis for women 35 years of age and over without prior screening. This right would be protected under strategy #3, with universal MSS and the choice of MSS or amniocentesis without prior screening for women 35 and over who want it. Almost 50% of DS cases would be diagnosed, with an iatrogenic fetal loss/case diagnosed ratio of 0.62, and a C/E ratio of $90,562 per case. The same approach, but with an age cutoff of 37 years (strategy #5), is more effective and has a lower C/E ratio ($79,664).

The best approach should be one that offers maternal serum screening to all pregnant women, maximizes the detection rate and minimizes iatrogenic fetal loss, allows women to make an informed choice and participate voluntarily, and preserves existing rights which, in Quebec, include the right to amniocentesis as of age 35.

CONCLUSION

The following conclusions were reached after this evaluation, which is supported by an in-depth review of the literature and a comparative analysis of various approaches to the screening and diagnosis of Down syndrome:

- *The Conseil considers that prenatal screening for Down syndrome using maternal serum markers should be made available to all pregnant women in Quebec, regardless of age.*

- *The participation of the pregnant woman in screening should be voluntary and based on informed choice, relying on complete, high quality information provided by first-line health care professionals (physicians, nurses, midwives, etc.) familiar with prenatal screening, and its benefits and limitations (false positive and false negative results).*

- *A woman's decision to undergo amniocentesis once prenatal screening indicates a high risk of Down syndrome or another chromosomal abnormality should also be voluntary and based on informed choice, relying on complete, high quality information provided by professionals trained in genetic counselling.*

- *The best screening strategy is one that permits more cases of Down syndrome to be diagnosed with the lowest risk of iatrogenic fetal loss at an acceptable cost. Selection of an age cutoff point for amniocentesis without prior screening should take existing rights into account, as well as the anxiety brought about by the possibility of having a child with Down syndrome for women aged 35 years and over.*

- *The screening and diagnostic strategy adopted for Down syndrome must be flexible, so that it can adjust rapidly to new technological developments.*

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LIST OF ABBREVIATIONS

AFP:	α-fetoprotein
CI:	confidence interval
CVS:	chorionic villus sampling
DNA:	deoxyribonucleic acid
DR:	detection rate
DRG:	diagnosis-related groups
DS:	Down syndrome
FISH:	fluorescence in situ hybridization
FPR:	false positive rate
FSH:	follicle-stimulating hormone
hCG:	human chorionic gonadotropin
	α-hCG: α subunit
	β-hCG: β subunit
IQ:	intelligence quotient
LH:	luteinizing hormone
MoM	multiple of the median
MSS:	maternal serum screening
PAPP-A:	pregnancy-associated plasma protein A
PCR:	polymerase chain reaction
PPV:	positive predictive value
TP:	termination of pregnancy
TSH:	thyroid-stimulating hormone
uE3:	unconjugated estriol

GLOSSARY

Abortion: Interruption of pregnancy before the 20th week of gestation, which corresponds to a fetal weight of approximately 500 g. Abortion can be early (before the 12th week) or late (between the 12th and 20th weeks). In this report, the terms abortion and fetal loss are sometimes used interchangeably.

Aneuploidy: An abnormal number of chromosomes being present, either due to the absence of a chromosome or the presence of an extra chromosome. The normal human karyotype contains 46 chromosomes, comprised of 22 pairs of autosomal chromosomes and one pair of sex chromosomes.

Balanced translocation: Alteration in the structure of two chromosomes, without any change in the quantity of genetic material. An individual presenting with a balanced translocation is a carrier but is unaffected by the chromosomal aberration.

Detection rate: The sensitivity of the test – i.e. its ability to identify affected subjects. It is closely related to the selected risk cutoff point and the false positive rate, but is independent of the prevalence of Down syndrome.

False negatives: Affected cases that remain undetected when screened.

False negative rate: The proportion of affected pregnancies considered to be at low risk on screening.

False positives: Unaffected cases considered at high risk when screened. The false positive rate is the complement of the specificity of the test (1-specificity).

False positive rate: The proportion of unaffected pregnancies considered to be high risk on screening. This rate is independent of the prevalence of Down syndrome and is equal to the complement of the specificity of the test (1 - specificity).

Fetal loss: Interruption of pregnancy after the 20th week and before the fetus is viable. In this report, the term "fetal loss" is used interchangeably with "abortion" in view of the difficulty in establishing the actual time point of the event in a particular pregnancy.

High risk after screening: The estimated risk is equal to or higher than the selected risk cutoff point. The risk cutoff ratio generally used when screening for Down syndrome is between 1:250 and 1:385.

Iatrogenic fetal loss: In this report, iatrogenic fetal loss refers exclusively to the loss of an unaffected fetus due to procedures intended for the diagnosis of Down syndrome.

Meiosis: Cell reproduction that results in the formation of the gametes (the spermatozoon and ovum). Unlike autosomal cells which contain 46 chromosomes (22 different pairs of autosomal chromosomes and one pair of sex chromosomes), gametes obtained through meiosis are haploid – i.e. they only contain 23 different chromosomes.

Mosaicism: The combination of more than one cell line, one of which presents a free trisomy or a translocation. This generally involves non-disjunction after formation of the zygote (i.e., the fertilized egg resulting from the combination of the two gametes, the spermatozoon and ovum).

Multiple of the median (MoM): Concentration of a serum marker in a pregnant woman divided by the median value of the marker concentration in all pregnant women at the same gestational age, after eliminating pregnancies with pathologies that might affect serum marker levels. An abnormal value is determined by one or more multiples of the median value, depending on the particular test.

Non-disjunction: An error in cell division that occurs during meiosis and which, in Down syndrome, results in the formation of gametes with two chromosome 21's. Trisomy 21 occurs upon fertilization by a normal gamete possessing one chromosome 21. Non-disjunction is not restricted to chromosome 21 and can give rise to other trisomies or a monosomy.

Phenotype: Manifestation of an individual's characteristics or make-up resulting from the interaction between his or her genetic background and environment.

Risk: In this study, risk is represented by the relationship between the number of affected and unaffected pregnancies, expressed as a ratio (e.g. a risk of 1:20 indicates 1 Down syndrome pregnancy for every 20 unaffected pregnancies) or as a proportion (e.g. a risk equal to 1/21, or 1 affected pregnancy out of 21 pregnancies).

Risk cutoff (point): An arbitrary value, which distinguishes high and low risk on screening.

Screening: The identification of a health problem in apparently healthy individuals. In the context of this report, screening refers to tests administered to pregnant women to detect whether they are at high risk of having a child with Down syndrome. Detection of an elevated risk does not confirm the diagnosis, but does suggest the need for diagnostic tests. (See table on next page for a comparison between Screening tests and diagnostic tests.)

Trisomy: The presence of three homologous chromosomes, rather than two.

Unbalanced translocation: Alteration in the structure of two chromosomes, involving a change in the quantity of genetic material present; an individual with this kind of translocation is affected by the chromosomal aberration.

References: [7, 103, 141]

Differences between screening and diagnostic tests [64]

Screening Test	Diagnostic Test
Intended to identify a health problem in an apparently healthy population.	Used to identify a health problem in an individual presenting specific problems.
A positive result does not confirm the diagnosis. It indicates an elevated risk of the disorder being present, and suggests the need for diagnostic tests.	A positive result confirms the diagnosis and is an indication to treat the patient.
Carried out on all individuals in a group.	Carried out on one individual.

EXPLANATORY NOTES

EVALUATION OF TEST PERFORMANCE[1]

This section introduces some of the concepts essential to an understanding of the report. It presents the method used to evaluate the internal validity or performance of a test – i.e. its ability to identify a given disease.

		Individuals		
		Ill	Healthy	Total
Test result	+	TP	FP	TP+FP
	-	FN	TN	FN+TN
Total		TP+FN	FP+TN	TP+FN+FP+TN

TP: True positive result (the individual is ill and the test is positive)
FP: False positive result (the individual is healthy but the test is positive)
FN: False negative result (the individual is ill but the test is negative)
TN: True negative result (the individual is healthy and the test is negative)

Sensitivity: $\frac{TP}{TP+FN} \times 100$

The **sensitivity** of a test represents the proportion of ill subjects that the test is capable of detecting in the population. In this report, sensitivity is called the ***"detection rate."***

- ***Specificity***: $\frac{TN}{TN+FP} \times 100$

  The ***specificity*** of a test represents the proportion of healthy subjects confirmed as such by the negative result of the text. Its complement ***(1 - specificity)*** represents the ***proportion of false positive results***. In this report, the complement of the specificity permits estimation of the number of non-DS pregnancies considered at high risk (***false positive rate***). In such cases, the possibility of other pathologies or a dating error will be verified, and the pregnant woman will be counselled about the possibility of undergoing a diagnostic test.

- ***Positive predictive value (PPV)***: $\frac{TP}{TP+FP} \times 100$

  The ***positive predictive value*** of a test or the ***predictive value of a positive result*** indicates the probability of the individual being ill when the test is positive. In this report, it represents the proportion of actual DS pregnancies among those with positive results.

[1]The reference for this section is [64].

- ***Negative predictive value (NPV)***: $\frac{TN}{TN+FN}\times 100$

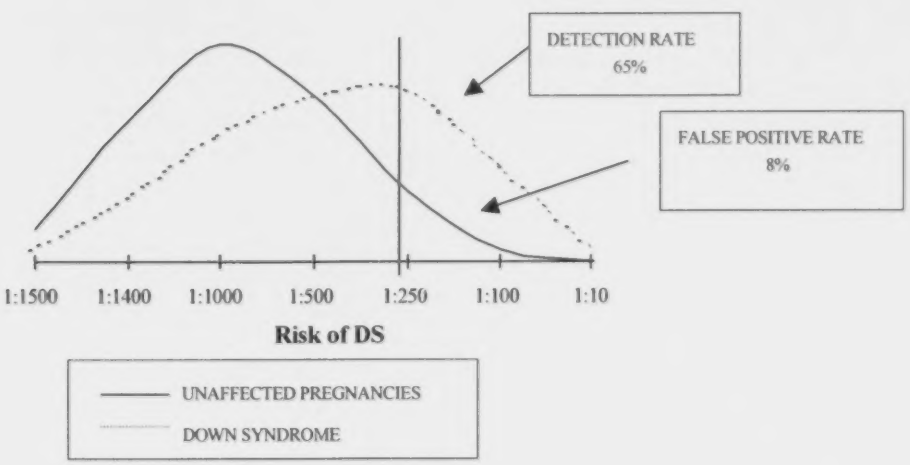
  The ***negative predictive value*** of a test or the ***predictive value of a negative result*** indicates the probability of an individual being healthy when the test is negative. In this report, it represents the proportion of non-DS pregnancies among those with negative results.

THE CONCEPT OF A RISK CUTOFF POINT

The selected risk cutoff point is closely related to the detection and false positive rates. Figure 1 shows the rates of detection and false positives for serum markers, based on a risk cutoff of 1:250. If the risk cutoff is shifted to the left (lower risk, e.g. 1:300, 1:385), the detection rate (sensitivity) improves, but with a concurrent rise in the false positive rate (1-specificity). If the risk cutoff is shifted to the right (higher risk, e.g. 1:200), fewer cases are detected by screening (lower detection rate), but there are also fewer false positive results.

Figure 1 represents the distribution of births and cases of DS expected in Quebec for year 2000, based on population projections [61] and the risk of DS at birth according to Cuckle et al. [34].

Figure 1: Detection and false positive rates using a risk cutoff point of 1:250



1. INTRODUCTION

Down syndrome (DS) is a common chromosomal abnormality, and the risk of having an affected child increases with maternal age. In Quebec and elsewhere in Canada, pregnant women aged 35 and over at time of delivery have had access to prenatal diagnosis for some years, using amniocentesis followed by karyotyping during the second trimester of pregnancy. However, amniocentesis is a costly, invasive technique, with risks for both mother and child. These drawbacks mean it cannot be used for all pregnant women who want to participate in prenatal diagnosis. Several non-invasive, prenatal screening techniques for DS are now available, and are based on the measurement of maternal serum markers or the use of ultrasonography. These permit the estimation of the individual risk of having a child with DS and, if this is considered high, amniocentesis is used to confirm the diagnosis. A number of Canadian provinces, as well as several countries in the world, have already made prenatal screening with serum markers available under national, provincial, or regional programs.

In this context, the *Ministère de la Santé et des Services sociaux du Québec* asked the *Conseil d'évaluation des technologies de la santé* to evaluate the introduction of a prenatal screening program for Down syndrome (DS) using serum markers. This report therefore addresses the effectiveness and costs of such a program in the second trimester of pregnancy, including diagnostic services such as obstetrical ultrasound and amniocentesis.

Chapter 2 addresses the clinical, genetic and epidemiological aspects of DS. Chapter 3 then presents a detailed description of screening and diagnostic methods currently available, together with their performance. This chapter also inclus des a brief discussion of several new technologies under development. In order to place prenatal screening in context, Chapter 4 provides a summary of current Down syndrome screening and diagnostic programs in Quebec, elsewhere in Canada and in other countries.

Particular attention has been paid to the ethical issues raised by the introduction of a prenatal screening program for DS, and by the analysis itself. Ethical considerations are discussed throughout the text, as well as in a specific chapter (Chapter 5). We also address the issue of risks associated with the diagnostic procedures and the fundamental importance of genetic counselling in helping women and couples make an informed decision. The discussion of the ethical issues involved in screening for Down syndrome clearly shows that any decision to take part in a screening program must be based on a personal, voluntary and informed choice. For this reason, we have preferred to speak of screening "access" or "strategy" in this report, rather than screening "program."

Chapter 6 presents a cost-effectiveness analysis of screening for Down syndrome using serum markers. Various DS prenatal screening and diagnostic approaches are first discussed. Baseline data for the variables used in the study are then presented, followed by the results of the cost-effectiveness analysis of serum marker screening and diagnostic amniocentesis, all based on Quebec and/or Canadian data.

Finally, Chapter 7 discusses some fundamental elements that should be considered when adopting a prenatal screening strategy, followed by the conclusion and recommendations.

DESCRIPTION OF DOWN SYNDROME

2.1 GENERAL

Down syndrome (DS) is the most common severe chromosomal abnormality known. In 95% of cases, it is caused by the presence of an extra chromosome 21 and is manifested by multiple malformations, a specific phenotype and mental deficiency [7, 106].

The syndrome was first described in 1866 by the British surgeon, John Langdon Down, but it was not until 1958, following the development of new cytogenetic techniques, that the French pediatrician Jérôme Lejeune detected the presence of a trisomy – i.e. the presence of three chromosomes instead of two – at pair 21. Translocations and mosaicism are more rare and were discovered some years later.

Several factors are recognized as possible causes of DS. These include a genetic predisposition to nondisjunction, since this risk is much higher in families where cases of DS have already occurred. Other factors have been reported in the literature, such as abdominal radiation, viral infectious diseases and autoimmune disorders, mainly those associated with the thyroid. The increase in the incidence of DS with maternal age suggests that non-disjunction may be related to hormonal changes in older women. However, some authors favour multiple causality [106].

2.2 CLINICAL DESCRIPTION

There is no uniform clinical presentation in DS. The phenotype of affected individuals is characterized by slanting eyelids and hypertelorism. The ears are small, with dysplasia of the external auditory conduit, thickening of the nuchal fold, round face, small skull, 5th finger in-curved with hypoplasia of the 2nd phalanx, excessive laxness of the ligaments, muscular hypotonia, pelvic dysplasia and absence of the Moro reflex. Mental retardation is always present, ranging from severe deficiency to almost normal intelligence. The intelligence quotient (IQ) varies from 20 to 75, with a mean of 50. Growth and development are slow, and affected individuals have a mean height 2 standard deviations below average. DS children begin to walk between 2 and 4 years of age, and talk between 4 and 6 years. The delay in language skills is accentuated by hearing problems. Despite their slow development, affected individuals can demonstrate diverse talents, sensitivity and ability to socialize.

Fifty percent of those affected have severe physical abnormalities, mainly cardiac and gastrointestinal. Serious malformations that require surgical correction are often involved. Congenital heart disease is present in 28.5% of affected neonates. The most common abnormality is persistent atrioventricular canal, followed by atrial and ventricular septal defects, Fallot's tetralogy and patent ductus arteriosus. Duodenal obstruction, in the form of atresia, stenosis or an annular pancreas, is present in 2-3% of cases. Conversely, one-third of children born with duodenal atresia have DS. Other malformations can be found and are listed as follows, in descending order of frequency: club foot, cataract, imperforation of the anus, cleft lip and palate, Hirschsprung's disease[2] and meningomyelocele [7].

Although their secondary sexual characteristics are normal, males are generally sterile because of testicular interstitial fibrosis and hypoplasia of the seminiferous tubules. Females, on the other hand, can procreate, with a 50% risk of giving birth to offspring with DS. Affected individuals have a greater incidence of primary congenital hypothyroidism, thyroiditis and diabetes mellitus. The incidence of leukemia is 10-30 times higher than

[2] Segmental rectosigmoid dyskinesia due to localized agenesis of the Meissner and Auerbach plexuses, resulting in a dilation, sometimes massive, of the underlying colon (known as congenital megacolon).

in the general population. The immune system is depressed as a result of abnormal B lymphocyte function, abnormal distribution of the T lymphocyte subset and differences in the phagocytic function of polynucleated leukocytes [7].

Early aging is found, with senile dementia developing around age 40. The prevalence of Alzheimer-type dementia is far greater among individuals with DS, and symptoms occur earlier than in the general population [129].

2.3 EPIDEMIOLOGY

Incidence at birth in the general population is between 1 in 700 and 1 in 1,000 live births.

The risk of giving birth to a child with DS slowly increases with maternal age up to 35 years at the time of delivery, and varies from 1:1,578 at age 15 to 1:474 at age 34. The risk increases rapidly thereafter to 1:384 at age 35 and 1:112 at age 40 [34].

In Quebec, the proportion of births among women aged 35 and over was 12% in 1996 (Appendix A). Using the risk of DS at birth according to maternal age [34], 41% of expected Down syndrome infants were born to mothers in this age group.

In 1996, 89 infants with DS were born in Quebec; 59 affected fetuses had been diagnosed in utero [20]. In most cases, diagnosis was based on samples of amniotic fluid and, in five cases, the diagnosis was based on umbilical blood sampling.

Using the risk at birth based on maternal age (as calculated by Cuckle et al. [34]) and the age distribution of mothers at time of delivery in the Quebec population, the number of expected cases of DS in Quebec for 2000 can be estimated at 111 (Appendix A).

American data on 7.8 million live births in 17 states from 1983 to 1990 show a significant decrease (of 29%) in the prevalence of DS among women aged 35 and over (36.6/10,000 live births in 1983 versus 25.9/10,000 live births in 1990). However, no change was noted in the prevalence of DS among women under 35 years of age. The decrease may be attributable to the increased use of amniocentesis in the 35 and over age group in prenatal diagnosis [26].

Approximately 23% of DS pregnancies abort spontaneously between the second trimester and term [32], and 55% between the 10th week and term [82].

The survival rate for a DS infant at one year is 90.7%; at 30 years of age, it is 79.2%. In cases with heart defects, survival rate is 76.3% at one year, and 49.9% at 30 years of age [10].

Life expectancy at birth is considerably reduced when severe malformations are present; otherwise, it is 40-50 years.

2.4 GENETIC CONSIDERATIONS[3]

In 92-95% of cases DS is due to complete trisomy, with the presence of an extra chromosome 21, as the result of maternal non-disjunction or an error in cell division during meiosis of the germinal cells. The incidence of non-disjunction increases exponentially with maternal age, and is greatly elevated after age 35. In 95% of cases, the extra chromosome comes from the mother.

Four to six percent of DS cases present with a translocation between chromosome 21 and the other chromosomes. In most cases, a 14,21 unbalanced translocation is involved or, more rarely, a 21,22. Finally, 2-3% of cases result from mosaicism.

[3] The main references for this section are [7, 104, 107].

3. PRENATAL SCREENING AND DIAGNOSIS OF DOWN SYNDROME

Prenatal screening for DS is comprised of technological procedures that can be made available to all pregnant women in an effort to identify those most at risk of giving birth to an affected fetus. A test result higher than the selected risk cutoff point does not indicate that the fetus is affected, but does suggest the need for further tests to confirm or refute the diagnosis [110]. Prenatal screening can be done using:

a) blood samples to measure biochemical markers in the maternal blood – i.e. alpha-fetoprotein (AFP), alone or in combination with human chorionic gonadotrophin (hCG) and unconjugated estriol (uE3). Together, these three markers are what is known as the "triple marker test";

b) ultrasonography, which can be used for both screening and diagnosis [110].

Other serum markers can be used, such as inhibin A and PAPP-A (*pregnancy-associated plasma protein A*) during the first trimester, as well as the urine assay of β-core, a degradation product of hCG and, in particular, its β-hCG subunit [60].

Prenatal diagnosis of DS is used to determine whether the fetus is affected in women considered at high risk after screening, and is based on analysis of the fetal karyotype. The sampling techniques presently available to obtain fetal cells are amniocentesis, chorionic villus sampling (CVS) and percutaneous umbilical blood sampling [35]. These invasive techniques allow amniotic fluid or tissue containing fetal cells to be obtained for chromosomal, biochemical or genetic testing. Ultrasonography permits the indirect visualization of the fetus and the diagnosis of structural or anatomical abnormalities. It is used in conjunction with invasive diagnostic techniques to guide the sample collection. Another technique, which is still experimental, consists of detecting fetal cells in the maternal blood circulation.

When applied to a portion of the population that is automatically considered at high risk – as is the case with women 35 years of age and over at the time of delivery – these methods tend to be thought of as equivalent to screening. In this report, however, they are considered to be diagnostic – i.e. used to confirm that a fetus has DS after screening indicates high risk.

3.1 THE EFFECT OF MATERNAL AGE ON THE INCIDENCE OF DS, AND ITS IMPORTANCE WITH REGARD TO SCREENING AND DIAGNOSIS

The relationship between the incidence of DS and maternal age is well-established [59], and is the origin of screening based on maternal age. Although not really a technique in itself, this form of screening is designed to target a group of women considered at high risk and to refer them for prenatal diagnosis.

The effect of age was first documented by Penrose in 1933 [30]. Epidemiological studies later confirmed this finding, and permitted a risk to be estimated for each year of reproductive life [16, 34, 57] (Table A.1; Appendix A). The data also show that the age effect is independent of the mother's ethnic origin or region [67]. The risk increases slowly with maternal age until the mid-thirties, when it starts to increase more rapidly with each year of age (Figure A.1; Appendix A). At age 40, the risk is 1:112 compared to 1:384 at age 35 and 1:909 at age 30. Table 1 summarizes these data.

Table 1: Estimated risk of having a Down syndrome fetus at second trimester and term, according to maternal age

Maternal age	Risk at second trimester	Risk at term
30 years [32]		1:909 (0.11%)
35 years [32]	1:290 (0.34%)	1:384 (0.26%)
40 years [32]		1:112 (0.89%)
All women 35 years and over [96]	1:150 (0.67%)	

The risk is greater if calculated at the second trimester of pregnancy, the point at which amniocentesis is generally performed, since approximately 23% of affected fetuses abort spontaneously between the second trimester and term [32]. In women aged 35 and over as a whole, the mean risk of DS is 1:150 (0.67%) about halfway through the pregnancy. In other words, one case of DS is detected for every 150 amniocenteses performed on women in this age group [96].

In Canada and the United States, the age cutoff point for considering a pregnant women to be at high risk has been set to 35 years at time of delivery. Pregnant women aged 35 and over are therefore referred directly for cytogenetic diagnosis, whereas those under 35 are referred only if there is a family history of chromosomal abnormalities or other major indications [3, 21]. This age cutoff point is also used for genetic counselling on the risks and options available, as well as for the planning and coordination of prenatal diagnostic services.

This cutoff value was chosen in consideration of the fact that the risk increases rapidly as of age 35 and that, at age 35, the risk of fetal loss associated with invasive diagnostic procedures is virtually equal to that of giving birth to an infant with trisomy. Such a statement applies to amniocentesis (0.5 to 1% risk of iatrogenic fetal loss), but not to chorionic villus samping (CVS) which is associated with a higher risk of fetal loss (2 to 3%). In France and other European countries, such as Norway and certain regions of Portugal, Spain and Sweden, the selected cutoff is 37 to 38 years of age [75]. Regardless of the selected cutoff, this method considers the two results to be equivalent – i.e. the fact of having a child with DS and that of losing an unaffected child because of the procedure [104, 131]. However, some women may prefer to risk losing an unaffected child rather than to have a DS infant, even if their risk is low. Others may refuse amniocentesis, even though their risk is high [131].

Prenatal diagnosis based on maternal age has its limitations. Only one-third to nearly one-half of children with DS are born to women aged 35 and over. Although the individual risk is lower for younger women, women under 35 accounted for 92.5% of all pregnancies, and 69% of DS births, in the United States in 1993 [52]. Because of their age, virtually none of these women would have had access to prenatal diagnosis [131].

In Quebec, the proportion of births among women 35 years and over rose from 8% in 1991 to 12% in 1996 [120], and is expected to be 12.13% in 2000 (Table A.1; Appendix A) [61]. In Ontario, for the period 1979-1989, the percentage of women who gave birth rose by 40% for those aged 30-34, doubled for the 35-39 age group and increased by 45% for women aged 40-44 [65]. The proportion of live births for women aged 35 and over in British Columbi was 15% in 1996 versus 13.5% for the period 1992-96 [130].

Table 2: Estimate of detection and false positive rates for prenatal diagnosis with amniocentesis, Quebec, year 2000*

	Pregnant women, 35 years of age and over		
	Affected fetuses	**Unaffected fetuses**	**Total**
Referred for amniocentesis	46	9,050	9,096
Not referred for amniocentesis	0	0	0
	46	9,050	9,096
Detection rate: 46/46*100 = 100%			
False positive rate: 9050/9050*100 = 100%			
	All pregnant women		
	Affected fetuses	**Unaffected fetuses**	**Total**
Referred for amniocentesis	46	9,050	9,096
Not referred for amniocentesis	65	65,841	65,906
	111	74,891	75,002
Detection rate: 46/111*100 = 42 %			
False positive rate: 9050/74,891*100 = 12 %			

* The estimates are based on the expected distribution of births, according to maternal age, in Quebec in the year 2000, assuming a participation rate of 100 %.
Source: [34, 61, 62]

If each woman 35 years and over at time of delivery were to take advantage of cytogenetic diagnosis (using amniocentesis or CVS), the DS detection rate for this group would be practically 100%. In Quebec, screening based on the mother's age, followed by cytogenetic diagnosis, would be able to detect 42% of all cases of DS, assuming a participation rate of 100% and using the expected age curve for mothers at time of delivery in 2000 (Table 2).

In other words, amniocentesis would have to be performed on 9,096 pregnant women (12%) to detect 46 cases of DS (42%), with a false positive rate of 12% (9,050 amniocenteses/74,891 pregnant women). Furthermore, since amniocentesis presents certain risks, iatrogenic fetal loss is estimated at 0.5%, or the loss of 45 unaffected fetuses.

These calculations are based on a participation rate of 100% and do not take into account amniocenteses performed in Quebec for other indications, such as family or obstetric history in pregnant women under age 35. In 1996, approximately 80% (5,779) of the 7,224 amniocenteses performed in Quebec [20] were done so because of advance maternal age (based on information provided by A. Duncan, MD, in a personal communication, June 1998). Based on these data, it is estimated that 57% of pregnant women aged 35 and over participate in prenatal diagnosis.

3.2 DESCRIPTION OF THE VARIOUS SCREENING TECHNIQUES

3.2.1 Serum marker screening

The relatively low detection rate for the population of pregnant women as a whole, and the lim-

ited impact of screening based on maternal age, have left room for the development of other methods to identify pregnancies at high risk for DS and to improve outcomes among women in all age groups. Over the past ten years, various developments have taken place in the identification of different markers in the maternal blood, and new techniques have already been adopted into routine obstetric practice in many areas.

Screening based on the measurement of serum marker levels evaluates the individual risk for each pregnant women, which may be greater, equal to or lower than the risk estimate based only on maternal age. For women under age 35, serum screening offers the possibility of prenatal diagnosis when at high risk, and the option of continuing or terminating the pregnancy if the fetus proves to have DS. For women 35 and over, serum screening permits limitation of the number of diagnostic procedures and the associated risk of iatrogenic fetal loss. It can be used to detect DS, trisomy 18 (without additional tests on the same sample) and other open neural tube defects, such as spina bifida and anencephaly. On the other hand, closed neural tube defects cannot be detected.

Serum screening for DS began in 1984, when Merkatz et al. discovered (in a retrospective study) that the mean level of AFP (maternal serum alpha-fetoprotein) was lower in pregnancies affected by DS than in unaffected pregnancies. Likewise, AFP levels were higher, on average, in the presence of fetal open neural tube defects [84]. The AFP levels were independent of maternal age and the differences between affected and unaffected pregnancies were weak but consistent [33].

Marker test results are reported in multiples of the median (MoM) rather than mass units, in order to minimize factors contributing to variations among patients and centres (using different commercial kits, laboratory techniques, etc.). Combining data from 25 published case-control studies, Haddow et al. found that the mean level of maternal serum AFP in DS pregnancies was 0.75 MoM of the unaffected population [52].

It is estimated that screening based on AFP measurement only, at 15-22 weeks of gestation, detects approximately 20% of affected fetuses, at a false positive rate of 5%. Using a risk cutoff point of 1:380 – i.e. the risk for a woman aged 35 – the combination of maternal age and AFP measurement can yield an average detection rate of 33%, at a false positive rate of 5.1% [52]. At the same risk cutoff point, the detection rate varies widely according to maternal age, from 7% at age 25 to 83% at age 38 [52].

Despite its limitations, prenatal screening using AFP has rapidly been incorporated into practice in the United States [98], partly because it represents an extension of existing services for the detection of neural tube defects. Its feasibility was shown in a large-scale prospective study of screening based on maternal age and AFP measurement in women under age 35, with a DS detection rate of 25% and a false positive rate of 2.7% [91]. In 1985, Manitoba became the only Canadian province to offer a public program of prenatal screening using AFP, and it is estimated that the participation rate among pregnant women is 60% [28].

At the same time, other efforts to find more effective serum markers have resulted in two new possibilities: human chorionic gonadotrophin (hCG), present in DS pregnancies at twice (2.12 MoM) the level in unaffected pregnancies [14], and unconjugated estriol (uE3), reported to average 25% lower in DS pregnancies [24, 27]. Published data from 13 case-control studies indicate a mean of 0.72 MoM for uE3 in DS pregnancies [52].

Table 3: Detection rate (DR) and false positive rate (FPR) for various risk cutoffs, using a single marker combined with maternal age

	1:200		1:250		1:300	
	DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)	FPR (%)
AFP	29	3.1	34	4.4	37	5.7
UE3	35	3.4	40	4.7	46	6.3
Total hCG	46	3.9	49	5.0	53	6.4
α-hCG	33	3.3	38	4.8	40	5.7
β-hCG	37	2.6	45	4.0	56	6.5

Source: Wald et al. 1997 [141].

Based on the combined results of 21 published case-control studies, hCG measured during the second trimester is the most sensitive of the three markers, with a mean level of 2.12 MoM in cases of DS. hCG is made up of two covalently bound subunits, α and β, and more than 99% of hCG circulates in the blood intact. However, levels of both free α-hCG and free β-hCG are relatively high in DS pregnancies. The α subunit is identical to that of other pituitary hormones (e.g. LH, FSH and TSH), whereas the β subunit is specific to hCG [78]. When used for maternal serum screening, hCG is measured either in its intact or total form (intact + β subunit) [46, 79, 81, 82]. The choice of measure (i.e. intact or total) can influence the effectiveness of the screening [46].

Table 3 summarizes the performance of each marker individually, combined with maternal age. A detailed description of each marker is presented in Appendix B.

None of these three markers can be considered a diagnostic tool for DS. It is therefore inevitable that, at a given risk cutoff, a number of detected cases will be false positives, and that the great majority of these are selected for amniocentesis. In theory, serum screening can yield a detection rate of 100%, but only by generating almost 100% false positives. In practice, an acceptable compromise has to be reached between achieving the best detection rate possible and generating the lowest number of false positives.

3.2.1.1 Triple marker screening: AFP, uE3 and hCG

The combination of three markers (AFP, uE3 and hCG) form the basis of a method of MSS known as "triple marker" screening. This maternal serum test involves taking a blood sample from the pregnant woman between the 15th and 18th week of gestation. A 1992 survey of U.S. laboratories providing maternal serum marker services showed that 50% of the 4.2 million women who became pregnant in the United States that year participated in a screening program based on a single serum marker or a combination of markers [100]. Screening using various combinations of these markers is also widespread in the United Kingdom [139].

The triple marker test identifies pregnancies at risk for DS, as well as trisomy 18 without additional tests but using a different protocol. Trisomy 18 is the second most frequent abnormality after DS, with a prevalence of 1.2 cases per 10,000

births in Canada for the period 1991-1993 [65]. The triple marker test, however, does not detect other less common chromosomal abnormalities, such as trisomy 13 (prevalence in Canada: 1.2 per 10,000 births), sex chromosome-related aneuploidy (47 XXX, 47 XXY, and 45 X; revalence in Canada: 1.5 per 10,000 births), or other chromosomal problems which are only detectable with karyotype analysis [52, 65].

Wald et al. examined the use of the triple marker test as a population screening tool in a 1988 study [135]. The combination of the markers implies that each provides information on risk independently of the other components, including maternal age. Wald and colleagues showed no dependent relationship between the markers and maternal age, a weak correlation between certain markers and a strong correlation between others, e.g. total hCG and its free beta subunit. The authors also developed an analytic approach to calculate the individual risk based on the triple marker test (including maternal age). Setting the risk cutoff point at 1:250, detection levels for AFP, uE3 and hCG individually were estimated at 20, 25 and 40%, respectively, or 60% for the three combined, with a false positive rate of 5% [135].

The risk calculation for DS for each individual case is based on a combination of three variables:

a) the prevalence of DS in the pregnant population, including all ages;

b) the specific risk for a woman, given her age; and

c) serum marker values, adjusted for a certain number of variables.

These adjustments include consideration of the weak degree of interaction between the marker measurements, the method used to calculate gestational age and the correction for various factors that influence serum measurements, such as maternal weight, the presence of insulin-dependent diabetes, ethnic origin and cigarette smoking during pregnancy [132]. Such considerations apply only to singleton pregnancies, since a different approach is required when calculating the risk for multiple pregnancies [90]. In addition, recent data suggest a positive correlation between abnormally high or low levels of serum markers in consecutive pregnancies. This factor may account for some of the false positives obtained in serum screening [37, 58, 133]. The influence of each of these variables on marker levels is described in Appendix C.

An important element in the interpretation of maternal serum screening results is the accuracy of gestational age calculations. The levels of the three markers constantly change during the second trimester in all pregnancies (AFP and estriol increase, while hCG decreases), regardless of DS status [52]. An error in calculating the week of gestation significantly alters test performance. Overestimation of gestational age is reportedly responsible for nearly 50% of false positive results obtained with triple marker screening [54, 91, 134]. Accurate dating of the gestational age at the time the sample is taken may halve the number of pregnancies considered to be at high risk and thus referred to prenatal diagnosis.

Ultrasonography is the most reliable method to estimate gestational age, either by measuring biparietal diameter or crown-rump length [134, 143]. The traditional method of dating from the last menstruation can result in a error of two weeks in 15% of cases [51]. Current obstetric guidelines do not recommend the routine use of ultrasonography during prenatal care [38, 42, 124], even though the practice has become common in the United States.

Table 4: Triple marker detection rate (DR), false positive rate (FPR) and positive predictive value (PPV) according to the method used to estimate gestational age

Gestational age estimated by date			Gestational age estimated by ultrasound		
DR (%)	FPR (%)	PPV (%)	DR (%)	FPR (%)	PPV (%)
60	**5.8**	1.5	**60**	3.1	1.7
58	**5.0**	1.6	**67**	5.0	1.9

Table 5: Triple marker detection rate (DR), false positive rate (FPR) and positive predictive value (PPV) according to various risk cutoffs and method used to estimate gestational age, adjusted for maternal weight

Risk cutoff	Gestational age estimated by					
	Date			Ultrasound		
	DR (%)	FPR (%)	PPV (%)	DR (%)	FPR (%)	PPV (%)
1:150	49	2.8	2.3	58	2.6	2.9
1:200	54	4.0	1.8	62	3.6	2.3
1:250	**59**	**5.2**	**1.5**	**66**	**4.6**	**1.9**
1:300	62	6.4	1.3	69	5.5	1.6
1:350	**65**	**7.6**	**1.1**	**71**	**6.5**	**1.4**

Thus, the point at which serum screening is carried out is usually based on the date of the last menstruation and, if the result is positive, a reassessment is made using ultrasound [100]. This is the procedure used in the Ontario Maternal Serum Screening Program, which recommends ultrasonography to confirm the week of gestation in all cases considered at high risk after serum screening, in order to reduce the number of false positives [121].

Triple marker screening performance

No prospective study has examined the impact of accurate gestational age dating on detection rate. Wald et al. analyzed weekly variances in serum marker levels in 2,113 non-DS pregnancies and using previously-collected data for DS pregnancies [134]. This study showed that the use of ultrasound to calculate gestational age increased the detection rate from 58 to 67% (while holding the false positive rate at 5%) and reduced false positives from 5.8 to 3.1% (while holding the detection rate at 60%). The positive predictive value – i.e. the probability of having a fetus with DS given a positive test result – varied from 1.5 to 1.9%. These results are summarized in Table 4.

Table 5 presents triple marker performance based on several different risk cutoff points. Wald and colleagues mention that these results only apply to cases in which ultrasound is performed before risk estimation with serum screening [134]. When ultrasound is used for women considered at high risk after screening, an increase in false negatives may occur because of the re-classification of some positive

results to negative after gestational age correction For this reason, somescreening programs may adopt

Table 6: Triple marker detection rate (DR) and false positive rate (FPR) for various maternal ages and using a risk cutoff of 1:250*

Mother's age	Risk cutoff	DR (%)	FPR (%)
20 years	1:250	40	2.5
40 years	1:250	90	36
Under 35 years	1:250	48	3.7
35 years and over	1:250	87	23
General population	1:250	63	5.4

*These results have been calculated using the age distribution of the U.S. population in 1987.

Table 7: Study characteristics and results of an 11-study meta-analysis by Palomaki et al., 1996 [101]

Study characteristics			
Number of studies	11		
Markers used	Triple test: AFP, uE3, hCG		
Year of publication	1992-1995		
Origin of studies	5 U.S. studies 6 European studies		
Age of mothers	9 studies included all women 1 study included those under 35 years 1 study included those 30 years and over		
Risk cutoff point	1:200 to 1:380		
Detection rate	34 to 88%		
Amniocentesis participation rate	70 to 97%		
Meta-analysis results			
Detection rate (%)	57	64	69
False positive rate (0%)	3	5	7

a policy of not reclassifying positive results, unless the ultrasound scan shows a very pronounced difference in gestational age.

The detection and false positive rates can be presented for each specific age or as overall rates – i.e mean rates for all women regardless of their age.

Using a risk cutoff point of 1:250, the detection rate varies from 40% at age 20 to almost 90% at age 40, with a proportionate increase in false positive rates from 2.5 to 36%. If only two age categories are considered, the mean detection rate is 48% for those under 35 years and 87% for

those 35 years and over [52]. These results are summarized in Table 6.

In a recent meta-analysis of data provided by 16 published prospective studies on second-trimester DS screening, Palomaki et al. present a standardized approach for the evaluation of screening performance [101]. Eleven of the 16 studies involved the triple marker test (AFP, hCG and uE3). Detection rates varied across studies, and a number of factors that reduce reliability by overestimating the detection rate were described. These included failure to account for spontaneous loss of DS fetuses between the second trimester and term, as well as incomplete ascertainment of liveborn DS cases missed by screening. Other factors contributed to the variability among study results, such as the small number of DS cases in any given study due to low incidence, the use of different risk cutoff points, variations in age distribution among study populations and the use of different combinations of markers. After standardizing for these factors and combining the results of the 11 studies using the triple marker test (AFP, hCG and uE3), the overall detection rate was estimated as 64%, at an initial false positive rate of 5% [101]. The characteristics of the studies and the results of the meta-analysis are summarized in Table 7.

A second recent meta-analysis of 31 studies involving various combinations of three markers estimated the detection rate at 64% (95% CI: 59-68%) and specificity at 94% (95% CI: 93-95%). Meta-analysis of the studies that examined the triple marker detection rate including AFP, hCG (intact or total) and uE3 yielded a sensitivity of 64% (95% CI: 59-69%) and a specificity of 92% (95% CI: 90-94%) [43].

In addition, an evaluation of the results obtained during the first two years of the Ontario Maternal Screening Program showed a detection rate of 66%. The program uses a risk cutoff point of 1:384 and reports a false positive rate of 6% [97].

3.2.1.2 Other combinations of second-trimester serum markers

A number of studies have examined the performance of various combinations of serum arkers, and this varies depending on the risk cutoff point and the selected false positive rate. Table 8 summarizes the main results presented by Wald et al. [141].

A meta-analysis combining the results of 14 studies on the detection rate with AFP and free β-hCG found a sensitivity of 61% (95% CI: 56-67%) and a specificity of 95% (95% CI: 94-96%). This 2-marker combination presents the best results in terms of sensitivity and specificity [43].

Few studies have evaluated the performance of a variation on the triple marker method – a quadruple marker test – comprised of AFP, uE3, free α-hCG and free β-hCG, for example [137]. In a case-control study of 75 DS pregnancies, Wald et al. found that the quadruple marker measure increased the triple test (AFP, uE3 and total hCG) detection rate from 59 to 63% (a 6% augmentation) for a 5% false positive rate; at a constant detection rate of 60% and estimating gestational age with ultrasound, the false positive rate decreased by one-third, from 3 to 2% [137]. These results require confirmation with prospective studies. Other 4-marker combinations are possible, and some include measurement of inhibin A. Table 9 summarizes the results presented by Wald et al. [141], adjusting for maternal weight.

3.2.1.3 New developments in second-trimester screening

A number of placental products measured in maternal serum during the second trimester have been found at elevated levels in DS pregnancies, including human placental lactogen, Schwangerschaft Protein (SP or PAPP-C *Pregnancy-Associated Plasma Protein C*), inhibin and pro-

gesterone [68]. Of these, inhibin is the most promising marker and may become an alternative or additional marker for second-trimester screennig. Recent studies suggest that the performance of one particular form of inhibin, inhibin dimeric A, may be comparable to that of hCG and, in combination with the triple marker test, may significantly increase the detection rate [141, 146]. Prospective

Table 8: Detection rate for various 2-marker combinations together with maternal age, according to the risk cutoff and false positive rate

Marker combination	Gestational age estimated by					
	Date			Ultrasound		
	DR (%)	FPR (%)	Risk cutoff	DR (%)	FPR (%)	Risk cutoff
AFP, β-Hcg	46	3.3	1:200	51	3.5	1:200
	53	4.7	1:250	57	4.8	1:250
	58	6.0	1:300	61	5.8	1:300
AFP, hCG	52	4.3	1:200	57	4.4	1:200
	57	5.7	1:250	61	5.7	1:250
	60	7.0	1:300	64	6.9	1:300
AFP, uE3	39	3.6	1:200	50	4.0	1:200
	45	5.1	1:250	54	5.3	1:250
	49	6.6	1:300	58	6.6	1:300

Source: Wald et al., 1997 [141]

Table 9: Detection rate (DR) and false positive rate (FPR) of various 4-marker combinations together with maternal age, according to risk cutoff points and method used to estimate gestational age

Marker combination	Gestational age estimated by					
	Date			Ultrasound		
	DR (%)	FPR (%)	Risk cutoff	DR (%)	FPR (%)	Risk cutoff
AFP, uE3, α-hCG, β-hCG	59	3.2	1:200	66	2.9	1:200
	63	4.1	1:250	69	3.7	1:250
	66	5.1	1:300	71	4.5	1:300
AFP, uE3, hCG, inhibin A	64	3.9	1:200	72	3.5	1:200
	67	5.0	1:250	75	4.4	1:250
	70	6.0	1:300	77	5.2	1:300
AFP, uE3, hCG, α-hCG	58	3.6	1:200	67	3.5	1:200
	62	4.7	1:250	70	4.4	1:250
	65	5.7	1:300	72	5.3	1:300

Source: Wald et al. 1997 [141]

studies are necessary to confirm this performance on a larger scale.

Several study groups have examined the relationship between inhibin A concentrations and DS, using new inhibin A-specific immunoassay techniques. Although total inhibin and inhibin A increase in DS, it appears that the latter provides better discrimination of affected pregnancies [72]. Five published case-control studies report inhibin A levels varying from 1.59 to 2.6 MoM in cases of DS, for an average of 1.95 MoM, based on a combined total of 195 cases [1, 31, 72, 136, 145].

Table 10: Second-trimester screening detection rate (%) using inhibin A, alone or in combination, for a 5% false positive rate of 5%

Inhibin combined with other markers	Detection rate (%) with gestational age estimated by	
	Date	Ultrasound
Inhibin A only	44	44
Inhibin A + AFP, total Hcg	67	70
AFP, total hCG	*54*	*58*
Inhibin A + AFP, total hCG, uE3	70	77
AFP, total hCG, uE3	*59*	*67*
Inhibin A + AFP, total hCG, uE3, α-hCG	73	79
AFP, total hCG, uE3, α-hCG	*63*	*70*

The detection rates of the combined markers without inhibin A are shown in italics for comparison.

Moreover, Wald et al. found no correlation between inhibin A levels and maternal age [136]. In trisomy 18 pregnancies, inhibin A levels do not differ from those of normal pregnancies, indicating that this test would not contribute to detection of this disorder [1].

In a case-control study based on the analysis of serum samples from 77 DS pregnancies, Wald et al. estimated the detection rate with inhibin A alone or in combination with existing tests [136]. The results are presented in Table 10.

These detection rates were not corrected for maternal weight. If the gestational week is calculated by ultrasound, detection rates are 6-8% higher, except when inhibin A is used alone. Aitken and colleagues note that inhibin A concentrations change very little between the 15th and 18th week of gestation, the time period during which the second-trimester diagnosis is made. It therefore follows that accurate calculation of the gestational age will have much less impact on risk estimation with inhibin A than with other markers [1].

3.2.1.4 Serum screening during first trimester

The availability of first-trimester amniocentesis and CVS led to the search for reliable serum markers for the 8th to 12th week that were different from those used for screening purposes between the 15th and 18th week.

Several markers have been evaluated for first-trimester screening, including AFP, uE3, hCG and its subunits, pregnancy-associated plasma protein A (PAPP-A), placental alkaline phosphatase, cancer antigen 125, pregnancy-specific β-1 glycoprotein, dimeric inhibin A, progesterone and placental protein 14 [81, 142]. Of these, β-hCG and PAPP-A have shown the best results for use in first trimester. Median level of β-hCG at that time is significantly higher in DS pregnancies (1.73 MoM, based on 10 studies totalling 192 cases), while median level of PAPP-A is significantly lower (0.38 MoM, based on 12 studies totalling 251 cases) [140].

A recent prospective cohort study on 10,160 pregnant women in their 9th to 13th week of pregnancy reported a detection rate (95% CI) of 33% (11-55%), 50% (27-73%), 44% (11-67%) and 67% (45-89%) using maternal age only, maternal age plus β-hCG, maternal age plus PAPP-A, and maternal age plus β-hCG and PAPP-A, respectively, and holding the false positive rate at 10% [45]. The detection rates obtained in this study exclude spontaneous abortions occurring prior to the second trimester. A case-control study of 77 DS cases, among women who had undergone CVS because of their advanced age, confirmed the performance of β-hCG and PAPP-A. The detection rate using these two markers and maternal age was 63% (5.5% false positive rate and a 1:300 risk cutoff) [138]. These results suggest that screening during the first trimester is less satisfactory than during the second, since the detection rate for this older age group can be as high as 87%. However, the results cannot be compared to those for second-trimester screening without adjusting for spontaneous fetal loss, since 55% of affected pregnancies abort spontaneously between the 10th week and term [39, 82].

Wald and colleagues also considered the possibility that, for unknown reasons, positive results could be more frequent among pregnancies that terminated spontaneously than with those that continued to term [138]. Prospective studies should be carried out to test this hypothesis [142]. The high rate of abortions and spontaneous losses of fetuses with DS means that a large proportion of cases identified by first-trimester screening do not reach term. Pregnant women are therefore faced with the decision whether to voluntarily terminate a pregnancy which would not have reached term anyway [70]. No data are available to assess the psychological effects for a pregnant woman faced with such a choice.

First-trimester screening raises other questions, such as the appropriate time point in the pregnancy for a woman to consult for the first time and for diagnostic tests to be available. Early diagnosis allows termination of the pregnancy at an early stage of development, but carries a higher risk of fetal loss as a result of invasive diagnostic procedures. First-trimester amniocentesis (between the 11th and 12th week) has revealed potentially high risks, including the risk of fetal loss, club foot, loss of amniotic fluid and cell culture problems for karyotyping [22]. Moreover, chorionic villus sampling is rarely used in Quebec, and is associated with a higher rate of complications than second-trimester amniocentesis.

Serum screening during the first trimester does not permit the detection of neural tube defects. If serum screening is to be used rather than ultrasound to detect such malformations, a second screening is required to measure AFP during the second trimester.

3.2.2 Screening with ultrasound

Ultrasonographic technique is described in Appendix B. There is no specific diagnostic image for DS and a number of the typical structural changes occur at an advanced stage of pregnancy [77, 96]. The most useful ultrasound signs are based on subtle variations in the size of the fetal structures, such as nuchal thickness and length of the long bones. Other signs are less specific and appear later, such as a double gastric halo (possible pyloric stenosis) and cysts of the cerebral choroid plexus.

Screening with ultrasound uses two approaches: (1) measurement of the nuchal fold, combined with serum markers, during the first trimester of pregnancy, and (2) detection of cardiac abnormalities, translucency of the nuchal fold and shortening of bones in the limbs during the second trimester. The latter approach requires great expertise and access to sophisticated equipment [11, 127, 128].

Studies on the performance of nuchal translucency measurements during first-trimester screening have reported a strong association between the thickness of the nuchal fold (greater than 3–4 mm), assessed between the 10th and 13th week of pregnancy, and the risk of DS. The extent of this association is not clear, since several studies have not reported the amount of increase in nuchal fold thickness or the gestational week at which the examination took place [69]. Other authors point out the technical difficulties of reproducing the measurements obtained [109]. The detection rate for malformations found by ultrasound screening appears to be related to the time allowed for the examination, the standardization of procedures and the expertise of the professionals involved [73].

The first large-scale prospective study on screening based on maternal age and nuchal translucency reported a detection rate of 85%, for a 4.5% false positive rate [93]. Other authors have obtained results that are similar [102] or substantially lower [53, 69, studies cited by 140]. Recently, a multicentre prospective study of 83,000 pregnancies in the 10th to 14th week of gestation yielded a detection rate of 85%, with 11% false positives [94, 95]. According to other researchers, adjustment for spontaneous abortion and other important variables would bring the detection rate down to 58% [49]. A similar finding was observed in a study of 96,127 pregnancies, using maternal age and nuchal translucency between the 10th and 14th week of gestation: the detection rate was 82%, with 8.3% false positives, but only 60% after adjustment for spontaneous fetal loss [50, 119].

Debate on the performance of ultrasound screening for DS continues. However, the fact that several studies have reported a good level of performance suggests the need for new, well-structured studies to confirm this finding [12]. Nuchal translucency, either on its own or combined with serum markers, may provide an interesting option for first-trimester screening [17, 18].

3.2.3 Prenatal screening: conclusion

The primary purpose of prenatal screening is to identify pregnant women at high risk of giving birth to an infant with DS. Diagnostic methods can subsequently be used to confirm or refute the presence of a DS fetus among high risk women. Screening can be performed during the first or second trimester.

First-trimester screening using serum markers and ultrasound shows interesting results, with detection rates as high as 80% and a false positive rate of 5% when combining nuchal translucency, levels of β-hCG and PAPP-A and maternal age. However, the rates in most studies are comparable to second-trimester results. Although first-trimester screening makes earlier diagnosis possible, the use of diagnostic methods during this trimester represent a greater risk for both mother and fetus. In addition, AFP testing during the first trimester does not detect neural tube defects. Finally, since approximately 25% of DS pregnancies terminate spontaneously between the 10th and 15th week, the number of amniocenteses and voluntary terminations of pregnancy would be needlessly high.

Second-trimester screening can be done using serum markers or ultrasound. A number of markers have been studied in various combinations. The combination of three markers (AFP, hCG et uE3) forms the "triple-marker" test. The numerous evaluations of the effectiveness of screening with this technique generally report a global detection rate of 65%, for a 5% false positive rate At a risk cutoff between 1:250 and 1:380. This widely-studied test has been adopted for most screening programs, with variations (e.g. measurement of total or intact hCG or its α and β subunits). Ultrasound can either be combined with serum testing to confirm gestational age or used as a screening technique itself. However, sophisticated equipment and highly trained personnel must be available if this approach is selected for screening during either the first or second trimester, as well as standardization of ultrasonographic signs. New serum markers are currently under study. Although some appear very promising (e.g. inhibin A and PAPP-A), all need to be validated before their use can be recommended.

3.3 Prenatal diagnosis

Prenatal diagnosis of DS is performed by analyzing the karyotype of the fetal cells obtained by amniocentesis or CVS. These techniques are described in Appendix B. Prenatal diagnosis can be used for pregnant women at high risk given their age at time of delivery or for those identified as high risk as a result of one of the screening methods described previously.

3.3.1 Second-trimester amniocentesis

Amniocentesis was developed in the mid-1960s, and involves the aspiration of fetal cutaneous cells that have been shed for definitive diagnosis of DS and other chromosomal abnormalities. The fetal cells are cultured and manipulated to obtain a karyotype – i.e., a complete map of the chromosomes. Simultaneous ultrasound is essential when collecting the sample. Amniocentesis has now become a standard procedure for prenatal diagnosis during the second trimester; its use during the first trimester is in the experimental phase.

Amniocentesis also allows diagnosis of other aneuploidies related to maternal age, such as trisomy 13 and sex chromosome abnormalities (47 XXX, 47 XYY, 47 XXY and monosomy X). The use of ultrasound during amniocentesis permits the detection of other fetal abnormalities [96, 132].

The sensitivity and specificity of amniocentesis for DS surpasses 99%. This was confirmed during a randomized trial in the early 1980s involving 2,239 low-risk women who had undergone amniocentesis [122]. All cases of DS were detected

(4 cases, or 0.17 % of the amniocenteses). The *US Preventive Services Task Force* has reviewed all clinical trials on amniocentesis and reports no false positive results [123]. The Canadian Task Force on the Periodic Health Examination reported that approximately 1% of amniocenteses in three randomized trials had to be repeated because of problems with sample quality [38]. Despite the excellent reliability of amniocentesis and its related tests, errors can always occur. A U.S.-wide survey in the early 1980s reported diagnostic errors in 0.11 to 0.22% of cases because the cultured cells were maternal rather than fetal, due to contamination while the sample was being collected [48].

Maternal risks associated with the procedure include infection and vaginal leakage of amniotic fluid. Amnionitis, a serious but rare complication (1 in 1,000), can lead to loss of the fetus although, with appropriate antibiotic treatment, represents no danger to the mother [41]. Elias et al. reported no cases of hemorrhage or intra-abdominal lesion in 20,000 amniocenteses performed over a 20-year period [41]. Minor complications are more common. In 2-5% of cases, there is some spotting or vaginal leakage of amniotic fluid, uterine contractions and abdominal pain [38, 41]. Leakage of amniotic fluid can persist and eventually cause loss of the fetus.

The risk of fetal loss following amniocentesis is not known with certainty but is estimated to be 0.5-1%. An evaluation of this was carried out in Denmark between 1982 and 1984 in a randomized trial comparing amniocentesis with ultrasound among 4,600 low-risk pregnant women (under 35 years of age and with no risk factors for DS) [122]. The rate of spontaneous fetal loss after the 16th week (the time point at which amniocentesis is generally performed) was estimated to be 1.7% in the study group and 0.7% in the control group; that is, it was 1% higher following amniocentesis (the excess in the study group was 0.8% for the full pregnancy). Most fetal losses following amniocentesis occur within three weeks of the procedure being performed. The authors noted that the study underestimates the effect of amniocentesis, since a further 0.5% of pregnancies were voluntarily terminated post-amniocentesis because of detected abnormalities. It is generally accepted that the affected fetuses have a greater likelihood of intrauterine death had they not been aborted by choice, which would tend to increase the rate of spontaneous fetal loss following amniocentesis.

Other risks to the fetus during amniocentesis are puncture injury, infection and possibly isoimmunization [123]. Newborn respiratory distress syndrome was also reported in the Danish study [122], with 1.8% of infants born with either respiratory distress syndrome or pneumonia after amniocentesis versus 0.8% among newborns in the control group.

3.3.2 First-trimester amniocentesis

In the mid-1980s, physicians began using amniocentesis for early prenatal diagnosis during the first trimester, as a possible alternative to CVS. Technically, the procedure is identical to that performed during the second trimester. The difficulty with amniocentesis before the 13th week of gestation is the small amount of amniotic fluid available in the uterine cavity, which increases the risk of fetal injury. In a study using a genetic data base, each woman who had early amniocentesis (at 11-14 weeks of gestation) was compared with two others who had the procedure during the second trimester (at 16-19 weeks of gestation) [19]. All of the amniocenteses were performed by the same three physicians. In the early amniocentesis group, there were 9 cases (2.9%) of amniotic fluid leakage and 6 cases (1.9%) of vaginal bleeding, compared to 0.2% for both of these complications in the second-trimester group. There were 7 cases (2.2%) of fetal loss in the early amniocentesis group and 1 case (0.2%) in the second-trimester group. Four of the seven cases of fetal loss in the

early group occurred in women presenting immediate amniocentesis-related complications. The one woman who experienced fetal loss after amniocentesis in the second-trimester group presented no complications following the procedure.

The most recent data on the comparison of first- and second-trimester amniocentesis come from a Canada-wide, multicentre, randomized study of 4,374 pregnant women. The results show a significant increase in fetal loss for first- versus second-trimester amniocentesis (7.64 versus 5.92%; a difference of 1.72%, one- sided 95% CI: 2.98%, p=0.012), along with a significant increase in club foot (*talipes equinovarus*) (1.3 versus 0.1%, p=0.0001) and in amniotic fluid leakage (3.5 versus 1.7%, p=0.0007) [22].

The only randomized study to compare early amniocentesis and chorionic villus sampling (CVS) shows a significantly higher spontaneous fetal loss rate with early amniocentesis (5.9 versus 1.2%) [92]. In a non-randomized study, 3.6% fetal loss was reported after early amniocentesis compared to 2% following CVS [116]. Unlike Brumfield et al. [19], this latter study found no fetal loss related to complications occurring immediately after the procedure.

With respect to the possibility of obtaining better results from an early amniocentesis karyotype as opposed to one from CVS, two studies report either equivalent cytogenetic failure rates of under 1% [116], or better performance by amniocentesis, with a 3.4% rate of repeating the procedure versus 6.2% for CVS [115].

3.3.3 Chorionic villus sampling

Chorionic villus sampling (CVS), which was developed in the late 1960s, requires the collection of fragments of placental chorionic tissue to obtain viable cells that will be cultured for cytogenetic analysis [83]. It has the advantage of enabling prenatal diagnosis during the first trimester, even though it does not permit the diagnosis of neural tube defects. The Canadian Task Force on the Periodic Health Examination reviewed six case series including some 6,500 women [38]. More than 99% of women at high risk for DS were given the correct prenatal diagnosis, but subsequent amniocentesis was required in 5% of cases because the CVS results were inconclusive.

CVS presents two problems: (1) there is a greater risk of contamination by maternal cells, and (2) in 1% of cases, mosaicism is detected because of cytogenetic anomalies of the placental tissue itself, although these are not necessarily related to fetal abnormalities. The performance of amniocentesis subsequent to CVS increases the risk of fetal loss and creates additional anxiety for the parents in the time between the tests. Women may decide to terminate their pregnancy before receiving the amniocentesis result, even though there would be sufficient time for this procedure after the test. Having to repeat an amniocentesis, on the other hand, leaves far less time for such a decision.

The maternal risks are the same as those for amniocentesis, that is, leakage of amniotic fluid, hemorrhage, infection and intra-abdominal lesions [38, 41]. Three randomized trials estimated the risk of spontaneous fetal loss following CVS in comparison with amniocentesis in women at high risk of DS, either because of their age or history. The rate of spontaneous fetal loss before the 28th week of gestation was higher after CVS in all studies, with the difference varying between 1.7 and 2.9%. The best estimate available comes from two studies, one Canadian and one European, which report a statistically significant odds ratio of 1.32 (95% CI: 1.11-1.57) [38]. Analysis of the WHO-sponsored CVS registry, containing 138,966 pregnancies in 1994, documented a 2 to 3% spontaneous abortion rate following CVS for the 63 participating centres, with a mean rate of 2.48% [71]. The lowest rates were reported by

centres carrying out the greatest number of CVS procedures.

Fetal loss was evaluated in three randomized trials comparing transcervical and transabdominal CVS. In two of them, including more than 5,000 women, no difference was found between the two groups [15, 63]. The third study of 2,882 women in Denmark found a significantly lower risk of fetal loss with transabdominal CVS (3.7 versus 7.7%) [118]. A retrospective analysis in a single U.S. centre also reported greater losses with transcervical CVS, but found improvement in both techniques over time [29]. Transcervical CVS began in this centre in 1984; transabdominal CVS followed four years later. At that time, the risk of spontaneous abortion was greater for transabdominal procedures but, five years later, the risk was half that for the transcervical procedure. However, this study was not randomized and could be subject to selection and other biases. It does, however, add weight to the theory that there is a greater risk of fetal loss with transcervical rather than transabdominal CVS. The latter is also the faster procedure and is more comfortable for the mother [15, 118].

The most serious problem with chorionic villus sampling is an increase in fetal limb defects. This has been shown by two out of three registry-based case-control studies and other case-series investigations, but has not been observed in randomized or cohort studies. An analysis of the WHO CVS registry focused on the incidence of limb deformities [71]. Including minor nail malformations, the incidence was 5.7 per 10,000, based on 138,996 pregnancies, and 5.2 per 10,000 when nail defects were excluded. Other population-based studies which did not take prior CVS into account report an incidence of 4.8 to 5.97 per 10,000. Although the difference does not seem large overall, the rate of limb malformation following CVS was higher in some centres that also had a higher rate of fetal loss, probably due to lack of experience and inferior technical quality. The absence of randomized, large-scale studies, however, means that these results cannot be confirmed. Lastly, it is also interesting to note that there may be an inverse relationship between risk and gestational age at the time CVS is performed.

3.4 New technologies

3.4.1 Fetal cells in maternal blood

Researchers have been trying since the 1970s to develop a method for identifying fetal cells in maternal blood, in order to carry out genetic tests on fetal DNA. Several methods are now available, and this technology may rival amniocentesis and CVS in years to come, or even replace them (Appendix B). Its main advantage lies in the fact that fetal cells, mainly nucleated erythrocytes, can be obtained by non-invasive methods (a sample of maternal blood taken from a peripheral vein). No specialized experience is required on the part of the technician, thus avoiding the risks to mother and fetus. It is estimated that there is one nucleated fetal erythrocyte per 10^7 to 10^8 maternal blood cells [105, 117]. However, no fetal karyotype can be obtained with this type of cell, and other expensive techniques have to be used to detect chromosomal abnormalities: PCR (polymerase chain reaction) and fluorescence in situ hybridization (FISH), which are already used in cytogenetics. At this time, it is impossible to predict when and how this test may become generally available [74], but it could eventually replace maternal serum marker tests.

3.4.2 DNA analysis using amniotic fluid

Fluorescent (PCR) DNA analysis of amniotic fluid obtained via amniocentesis would permit diagnosis of DS as effectively as a karyotype, but in a very short period of time (approximately one day). In a recent prospective study of 2,139 amniotic fluid samples, 99.6% were correctly classified and all cases of DS diagnosed were confirmed by cytogenetic analysis. This method can

identify trisomy 21 as well as unbalanced translocations involving chromosome 21, but cannot differentiate between the two abnormalities. It is an automated technique, thus permitting analysis of 36-96 samples at the same time [126]. It is important to note that, for the same risk of fetal loss associated with collection of amniotic fluid, PCR analysis of DNA is less valuable than fetal karyotyping, as only DS can be identified.

3.5 Risks associated with termination of pregnancy (TP)

Termination of pregnancy (induced abortion) presents little serious risk. It appears to be responsible for 0.4 maternal deaths per 100,000 procedures. There is a lower risk of complications, such as infection, hemorrhage or other injury, if the procedure takes place during the first rather than the second trimester [38, 123]. Although complications occur more frequently during the second trimester, they are still rare in general.

A retrospective study, using semi-structured interviews, examined the psychological effects of TP in 48 women who had the procedure during their second trimester following prenatal diagnosis of a neural tube defect or chromosomal abnormality. Thirty-seven of the 48 women (77%) experienced an acute grief reaction, similar to that felt in cases of stillbirth and neonatal death [76]. A retrospective study used the same interview questionnaire for 69 women in the United Kingdom in 1989. The results showed that 55 women (80%) had an acute grief reaction and, in 19 cases (28%), the reaction was described as severe [40]. A Quebec study compared reactions of parents six months after termination of pregnancy in an experimental group of 76 women referred for prenatal diagnosis because they were high-risk, and a control group of 124 women in whom an abnormality was diagnosed during routine ultrasonography. The mourning reaction was lengthy in both groups, and 82% of women stated that they were still experiencing it at the time of the interview. Feelings of guilt were far more common in control group parents (73 versus 29%) for whom the diagnosis was unexpected. Parents in both groups would have liked to have had more time to decide whether to terminate the pregnancy [36].

3.6 The importance of genetic counselling

Prenatal screening for DS provides an estimate of the risk of having an affected child and, when this is considered high, prenatal diagnosis can be used to obtain a definitive result. The diagnostic methods present certain dangers for both mother and fetus and, when faced with a DS diagnosis, termination of pregnancy is the only preventive measure available. The decision whether to have prenatal diagnostic tests presents two different risks: (1) the risk of having a child with DS, and (2) the risk of losing an unaffected child because of the diagnostic procedures. In light of this, if the mother or couple agree to prenatal screening, they must receive all of the information necessary to understand its implications. First-line genetic counselling can be provided by health care professionals who are not specialized in genetics. More specialized counselling by genetic specialists or counsellors should focus on assisting the parents in the interpretation of screening results if a high risk is indicated, and helping them decide whether to proceed to prenatal diagnosis. Lastly, genetic counsellors should support the parents' decision to continue or terminate the pregnancy, and inform them of the risks associated with future pregnancies.

Genetic counsellors are health care professionals responsible for providing information and counselling to individuals or families at risk of having children who are affected by or carry genetic abnormalities. They must make every effort to help their clients reach the best decision, in a non-directive manner, and provide all information necessary for an informed decision appropriate to the individual case. Genetic counsellor training is available at two universities in Canada: one in Quebec and the other in British Columbia. At the present time, Quebec has five genetic counsellors within its public health system. One provides prenatal counselling full-time, while the others are involved to varying degrees. These figures do not include genetic counsellors in the private sector, nor those dealing with cancer. Genetic counselling in Quebec is generally provided by physicians, and is part of routine obstetric practice. In Ontario, which has had a maternal serum screening program for DS since 1993, there are now 34 genetic counsellors. Approximately 10 counsellors have been added since the provincial program was introduced (based on information received in July 1998 from Dr. A. Duncan, Director of the Cytogenetics Laboratory, Montreal Children's Hospital). As an indication, it should be noted that 10,303 amniocenteses were performed in Ontario in 1996, compared to 6,966 in Quebec during the same year [20].

4. THE CURRENT STATUS OF SCREENING AND DIAGNOSTIC PROGRAMS

This chapter provides a brief description of current DS screening and diagnostic programs in Canada, Quebec, and elsewhere. However, given the rapid development of the technologies in question, this information may soon be incomplete and is presented for indicative purposes only.

4.1 CANADA

Prenatal diagnosis has been available in Canada since the late 1960s. At that time, it was restricted to certain university hospitals and research centres in a few large urban centres.

Prenatal diagnostic services have been offered to Canadian women since approximately 1973, the year in which the first Canadian study to evaluate the safety and accuracy of amniocentesis in diagnosing chromosomal abnormalities began. Services then progressed with new knowledge and as new technologies became available. In 1993, the Royal Commission on New Reproductive Technologies identified 22 centres offering prenatal diagnosis in Canada [56, 110]. The Canadian College of Medical Geneticists (CCMG) includes advanced maternal age (i.e. 35 and over at time of delivery) as a clinical indication for prenatal cytogenetic diagnosis, as well as a positive serum screening test when a provincial maternal serum screening program is in place [21].

4.2 QUEBEC

Since 1976, prenatal diagnosis has been available to pregnant women at high risk of having a child with (a) a chromosomal abnormality, based on family or obstetric history, when the mother is 35 or over at the time of delivery; (b) a metabolic disorder, based on family history or because one or both parents are known carriers of the disorder; and (c) a neural tube defect, based on family or obstetric history [35].

Prenatal diagnosis (amniocentesis during the second trimester) is provided free of charge in Quebec, based on the advanced age of the mother and/or family/obstetric history. Amniocentesis is available in all hospitals with obstetric departments. Amniotic fluid samples are forwarded to one of three laboratories that specialize in culturing fetal cells and cytogenetic/ metabolic analysis. Maternal serum marker testing is still restricted to ongoing research programs. A private clinic in Montreal provides genetic screening and diagnostic services.

The referral rate[4] to prenatal diagnosis for women 35 and over was 64.5% in 1990, and it is estimated that 95% of those referred for amniocentesis agreed to the procedure [110]. A Quebec study carried out in the Lac-Saint-Jean region on 508 amniocenteses performed over a six-year period (1984-1990) showed that the most common indication was advanced age (62 %) and that, of the 14 abnormal results obtained, 10 led to termination of the pregnancy. The remaining four cases included three balanced translocations, with no termination of pregnancy, and one intrauterine death followed by spontaneous fetal loss [55].

4.3 ONTARIO

The Ontario Health Ministry set up a pilot project in July 1993 to provide DS triple marker serum screening to all pregnant women in the province [25]. Today, all pregnant women in Ontario have access to screening between the 15th and 17th week of pregnancy, and it is estimated that 50%

[4] The referral rate represents the proportion of pregnant women with a clinical indication for prenatal diagnosis who were actually referred to prenatal diagnostic services by their physician.

of them take advantage of it. Preliminary data indicate a detection rate of 73.5% at a false positive rate of 9.5% [46]. When screening indicates high risk (greater than 1:385), the woman is offered an ultrasound to confirm gestational age and a genetic counselling session, in order to explain the meaning of a positive result and allow her to make an informed decision regarding the various options available. The latest published results confirm a detection rate of 66% at a 6% false positive rate over a two-year period [97].

Serum tests are performed in seven designated laboratories across the province. A steering committee is responsible for the quality of these laboratories, and has established uniform standards with respect to medians, analysis and interpretation of results, and presentation of reports [121].

A survey of physicians and midwives assisting deliveries in Ontario revealed that nearly all of these health care professionals provide screening for their patients, but that their knowledge about the test was quite limited. For example, respondents overestimated the detection rate and underestimated the false negative rate. In addition, while 50% of respondents agreed with continuing the program as it now stands, 29% suggested modifications and 22% thought it would be better to stop it [25]. A recently-published Ontario study suggested the need to improve communication of the test results: 7.6% of the 1,117 women who underwent serum screening were not sure of their results when they were followed up at 24 weeks [47].

4.4 British Columbia

British Columbia provides prenatal cytogenetic testing, using amniotic fluid cells (obtained by amniocentesis) or chorionic cells, to all pregnant women aged 35 and over at the time of delivery, or 32 and over in the case of a multiple pregnancy. The indication also extends to any pregnant woman with a positive serum test, a family or obstetric history of chromosomal abnormalities, and those presenting with abnormal ultrasounds consistent with a chromosomal anomaly.

4.5 Manitoba

In 1985, Manitoba became the first Canadian province to offer a public prenatal serum screening program for all pregnant women, based on measuring alpha-fetoprotein (AFP) levels in maternal blood. Amniocentesis is offered to all pregnant women at high risk (risk cutoff of 1:384); women 35 and over are automatically considered to be at risk. A 1992 survey of general practitioners and obstetricians revealed that only 38% of respondents tested their patients after receiving consent, while 22% prescribed it routinely to all their patients [28]. Dr. Bernie Chodirker of the Department of Pediatrics, University of Manitoba, confirmed these data in a personal communication in March 1998, adding that Manitoba was currently considering adding the triple marker test to its serum screening program.

4.6 France

In France, as in most European countries, prenatal diagnosis using amniocentesis became available in the mid-1970s. Since 1980, testing has been paid for all pregnant women 38 years and over at time of delivery, for those with a family history of chromosomal anomalies, to diagnose gender in cases of sex-chromosome abnormalities, and in the presence of ultrasound markers such as morphological fetal abnormalities, intrauterine growth retardation or when an unusual quantity of amniotic fluid was present [8, 9]. In 1997, payment for pregnancies with a risk equal to or higher than 1:250 after serum screening was approved for a two-year period (renewable in 1999). Serum screening is established by law and subject to quality control at the national level. In addition, assay kits used for measurement must be certified. Serum screening was the subject of a pilot study of some 22,000 pregnancies in 1990-1991, following which the routine use of serum

lowing which the routine use of serum markers was proposed to the Health Ministry. The maximum number of laboratories authorized to perform the tests was set to 70 for France as a whole, covering about 700,000 births per year. In 1996, 30% of pregnancies were tested, compared to 15% in 1994, and this rate has increased considerably over the last two years. The rate of participation in screening and the rate of acceptance of amniocentesis for pregnancies at risk appears to be around 80%. When DS is diagnosed, 5% of women decide to continue the pregnancy. This information was obtained from Ségolène Aymé, Director of the Clinical Research Human Genome Mapping Department, SC11 INSERM, France (personal communication, April 1998).

4.7 Other European countries

A national program using maternal serum screening is also available in Italy. Prenatal screening is widespread in the United Kingdom, although coverage is not universal and services vary from region to region. In most cases, screening is based on AFP and hCG testing, together with maternal age; the use of the triple marker and AFP alone is less common [79]. In other countries, such as Belgium, Spain and Finland, screening is only available in certain regions [75]. In Belgium, where regional prenatal screening programs have been in existence since 1991, data from two regions indicate that the percentage of DS cases diagnosed prior to birth rose from 48% in 1991 to 71% in 1995 [125].

4.8 United States

In 1985, the American College of Obstetricians and Gynecologists (ACOG) published recommendations stating that all pregnant women should have access to prenatal AFP screening for neural tube defects. In 1994, ACOG recommended maternal serum screening for DS between the 15th and 18th week of gestation for all pregnant women under 35 years of age [3, 23]. AAP/ACOG (American Academy of Pediatrics/ American College of Obstetricians and Gynecologists) also recommended amniocentesis for women 35 years of age and over [2]. However, if a woman wants to avoid the risks associated with amniocentesis, she can have access to serum screening, although this was not recommended as an alternative to cytogenetic diagnosis at age 35 and over. A recent U.S. study revealed that two-thirds of pregnant women took advantage of maternal serum screening in 1995 and that this percentage continues to rise [99].

5. ETHICAL ISSUES

The prenatal screening and diagnosis of DS raises a number of ethical questions for pregnant women and/or couples, as well as for health care professionals, society and government.

5.1 PREGNANT WOMEN/COUPLES

DS screening and diagnosis do not provide any therapeutic solution; the only preventive action possible for the parents is to voluntarily terminate the pregnancy. The availability of these techniques means that pregnant women and/or couples are faced with difficult decisions that need to be made very quickly in mid-pregnancy, a period that is already charged with anxiety and emotion [112]. They must first decide whether or not to participate in screening. If an elevated risk is indicated, they must decide whether to continue on to diagnosis, knowing that the available methods are invasive and present risks to mother and child. Finally, they will be faced with either terminating or continuing the pregnancy if the diagnosis of DS is confirmed.

Participation must be both **voluntary** and **informed,** based on freedom of choice and the individual's prior, adequate understanding of all of the issues surrounding prenatal screening and diagnosis, its benefits and its consequences. It is, however, difficult to define what level of information is sufficient for someone to make an "informed" choice [66]. The parents must be aware of the limitations of the screening process and the complications associated with the diagnosis. They must also understand that the screening result expresses a risk and does not guarantee whether the fetus has DS or not. In a number of cases, screening will indicate high risk when the fetus is not actually affected, and the pregnant woman will be exposed to the complications associated with the diagnostic procedures. On the other hand, some parents will have a child with DS, even though the screening result indicated low risk.Once a DS diagnosis is confirmed, the decision must focus on whether to continue or terminate the pregnancy. In Canada, there is no provision in law regarding the decision to terminate a pregnancy since 1988 when the Supreme Court invalidated the abortion provisions of the Criminal Code in the Morgentaler case. None of the bills tabled since have been adopted. If the parents are opposed to abortion, prenatal screening and diagnosis represent one way to anticipate the abnormality and allow them to be better prepared for it at birth.

5.2 HEALTH CARE PROFESSIONALS

Health care professionals have a duty and obligation to inform pregnant women that screening tests are available. Genetic counselling professionals must provide information on the benefits, limitations and consequences of screening and diagnosis, in an **objective, non-directive** manner [89]. Genetic counselling must permit the pregnant woman or couple to decide whether to participate in screening after having received all of the information relevant to DS, the risk of having an affected child, and the risks and limitations of the screening and diagnostic procedures. Counselling should also consider the social aspects of the lives of people with DS [86].

Universal access to screening may make its prescription routine, and thus infringe on the principle of autonomy. Screening would then lose its purpose (i.e., to provide couples with informed options) and could take on eugenic overtones or create repercussions for those refusing to have the tests [6, 110]. At the same time, routine screening would also permit equal access, in order to eliminate differences in knowledge due to social class.

5.3 SOCIETY AND GOVERNMENT

Even if the possibility of abortion is accepted, prenatal diagnosis raises other ethical issues, such as the debate on the selection of which children should be born. In the case of DS, the diagnosis of an affected pregnancy gives no indication of the seriousness of the case – i.e. the degree of mental handicap and the presence or absence of DS-related malformations. Furthermore, the use of invasive diagnostic procedures also introduces the possibility of spontaneous loss of unaffected fetuses.

Selecting an age or risk cutoff point at which the use of diagnostic procedures is justified, based on the equal risk of giving birth to a child with DS and iatrogenic loss of an unaffected fetus, conveys the impression that these two events are equivalent for pregnant women [88]. In addition, the adoption of a risk or age cutoff point for screening/ diagnosis implies that a certain number of cases will not be detected or diagnosed.

The decision to make DS prenatal screening available is a prerogative of government, and should be accompanied by the will to provide all services considered necessary and to ensure their quality. In view of the importance of genetic counselling, particular attention should be paid to training professionals and to the resources assigned to this sector of clinical practice.

Each DS case that is avoided eases the economic burden for the community, particularly with respect to health care services and the specialized education required by affected children. But the identification of fetuses with a congenital disorder and the recourse to abortion reinforces prejudice against the handicapped and the image of the burden that affected persons represent for society in general, their families and, finally, themselves. Prenatal screening should not lead to the reassignment of resources and a decrease in services available to treat affected individuals or to support their families [86].

6. SCREENING AND DIAGNOSTIC STRATEGY

6.1 JUSTIFICATION FOR THE SELECTED APPROACHES

This study seeks to evaluate and compare various approaches to DS screening and diagnosis, in order to provide pregnant women with the most complete information on the available methods and to identify the most appropriate options from a cost-effectiveness perspective, without calling the relevance of the screening principle into question. We do not evaluate the negative cost represented by the loss of a normal fetus as a result of prenatal diagnosis, nor the social costs (mainly health care services and specialized education) arising from the care of individuals with DS.

Second-trimester screening based on serum markers is the only practical maternal serum screening option currently available. Second-trimester serum markers (AFP, hCG [total, intact or its α and β subunits] and uE3) form the most valid combination and the one most often used worldwide. The detection rate may be improved by the addition of a fourth marker or an additional inhibin A test.

There appears to be no consensus in the scientific literature regarding the usefulness of first-trimester markers nor the use of ultrasonography alone in prenatal screening for DS. Although results are promising, ultrasound screening requires the availability of sophisticated equipment, more time, and the additional costs associated with operator training and the maneuver itself. However, it is important to consider flexible screening strategies that can be easily adapted to changes in screening and diagnostic techniques.

Chorionic villus sampling during the first trimester and amniocentesis during the second are widely accepted as diagnostic methods, but CVS presents a higher risk than second-trimester amniocentesis and its use is limited in Quebec. The safety of amniocentesis during the first trimester has not been proved so that this cannot be considered as a viable alternative at present. If diagnosis is required following serum marker screening, second-trimester amniocentesis remains the only solution available.

The elucidation of various approaches to screening and diagnosis must be based on the following considerations:

1. Should all pregnant women have access to prenatal screening based on maternal serum markers?

2. Should women over a certain age have access to a diagnostic procedure (amniocentesis or chorionic villus sampling) without prior serum screening and, if so, what should be the cutoff age?

3. Should ultrasound technology be used routinely to estimate gestational age in all women, before proceeding with serum testing, or only for those at moderate or high risk based on a combination of serum screening results and maternal age?

Some decisions on the combination of services to be provided involve economic considerations. The question of ultrasonography is a good illustration of this. Prescribing multiple routine ultrasound examinations during the second and third trimester of pregnancy for women at low obstetric risk and no clinical indications is not recommended, since there is no evidence that this practice provides health benefits [5]. But neither the Canadian Task Force on the Periodic Health Examination nor its

Table 11: Approaches to the screening and diagnosis of Down syndrome considered in the cost-effectiveness analysis

Approach	Description	Abbreviation
1	Amniocentesis if 35 and over at time of delivery (current situation in Quebec)	Amnio 35 +
2	Universal MSS; amniocentesis if high risk after serum test	Universal MSS
3	MSS if under 35; MSS or amniocentesis if 35 and over (current situation in Ontario)	Universal MSS Amnio 35 +
4	MSS if under 35; amniocentesis if 35 and over	MSS <35 Amnio 35 +
5	MSS if under 37; MSS or amniocentesis if 37 and over	Universal MSS Amnio 37 +
6	MSS if under 37; amniocentesis if 37 and over	MSS <37 Amnio 37 +

MSS = maternal serum screening

U.S. counterpart haveexamined the benefits of using ultrasound to improve the performance of prenatal maternal serum screening, together with the associated costs. Ultrasonography is a risk-free procedure and, in the specific case of DS screening, the decision to use it is based on benefits obtained in relation to additional costs, apart from any other advantage it may represent.

The decision to refer a pregnant woman for amniocentesis or CVS should take into account the risk of spontaneous abortion or fetal loss and the complications associated with these procedures. This implies comparing the risk of having a child with DS to that of losing an unaffected fetus. In both the literature and in practice, there is no set risk cutoff point to define "high risk": it varies between 1:200 and 1:380 [101], depending on the performance of the method used, the age distribution of pregnant women in the population and the impact on diagnostic services available in a given area [46]. Wald et al. stress the economic impact of the selected risk cutoff in economic analysis [141]. In effect, detection rates improve with lower risk cutoffs, but the total cost of screening rises because of the greater number of false positives and number of amniocenteses performed.

Do we need to alter the current practice of offering amniocentesis to all women aged 35 and over at time of delivery, a system that was developed and put into effect prior to the advent of serum marker tests? The answer to this question must consider detection and false positive rates, iatrogenic loss of unaffected fetuses and the associated costs.

The various approaches used to screen for and diagnose DS were analyzed by first looking at the current situation – i.e. amniocentesis offered to women aged 35 and over at time of delivery. This

approach and the others put forward, some of which are in use elsewhere, are given in Table 11.

Table 12: Cost-effectiveness parameters: baseline estimates and parameter variations in the prenatal screening and diagnosis of Down syndrome

	Under 35	35 and over	All	Ref.
Number of births expected in Quebec in 2000	65,906	9,096	75,002	Appendix A
Cases of DS expected at birth, based on mother's age	65	46	111	Appendix A
Detection rate	48%*	87%*	65% (59-69)**	[43, 52, 101, 121, 141]
False positive rate	3.7%*	23%*	8% (6-10)**	
Screening participation rate	55%	55%	55% (50-60)	[28, 121]
Current amniocentesis participation rate (approach #1)***		60 %		[20]
Estimated amniocentesis participation rate	89%	80%	85% (80-90)	[121]
Iatrogenic fetal loss rate	0.5%	0.5%	0.5% (1%)	[122]

* **For a risk cutoff of 1:250 and gestational age estimated by date**

** **For a risk cutoff of 1:385 and gestational age confirmed by ultrasound**

*** The participation rate considered for approach #1 (the current situation in Quebec) is 60%. The referral rate to a genetic diagnosis service appears to be 64.5%, and 89% of all women referred for amniocentesis agree to this procedure.

The parameters in **bold** print will be subject to a sensitivity analysis, using the estimated values given in parentheses.

Other approaches could be envisaged, such as MSS only being made available after certain age cutoff points, such as 30 years; in this case, the choice of age cutoff point would have to be justified.

6.2 Effectiveness of the Selected Approaches

Unlike a cost/benefit method, the cost-effectiveness analysis in this study avoids the difficulty of measuring the monetary value of the benefit(s) obtained. The effectiveness indicator is the number of "cases diagnosed." Although benefits can be assessed in terms of savings to the health care system, to the educational system and to the family for each birth prevented, such a calculation does not take into account the positive aspects of the life of someone with DS for themselves, their family and society in general, nor the suffering of parents of children with the disorder. In addition, a cost/benefit analysis based on costs avoided ignores the benefits in terms of reassurance and well-being provided by a negative examination for the future parents, as well as the consequences of falsely negative results [88].

Table 13: Costs used in the base case scenario, with probability intervals indicated for the purpose of the sensitivity analysis

	Cost (probability interval)	Ref.
Prenatal visit	$12.00	[108]
Medical visit	$29.30	[108]
Genetic counselling	$77.40 ($38.70 - $116.10)	[107]
Serum test	$26.16 ($20.00 - $60.00)	Appendix E
Obstetrical ultrasound	$25.00 ($20.00 - $60.00)	Appendix E
Amniocentesis	$468.28 ($400.00 - $500.00)	Appendix E

This analysis is done from the perspective of the public health care system. We therefore consider the costs associated with screening/diagnostic techniques and genetic counselling, without taking into account the costs or benefits of prenatal

DS screening for the families concerned or society in general [80]. The effectiveness of prenatal screening is its ability to identify affected fetuses, while costs are defined as the direct costs associated with the screening and diagnosis of DS. The cost-effectiveness ratio (C/E ratio) thus represents the cost per diagnosed case of DS. The iatrogenic loss of unaffected fetuses is considered, but the analysis does not take costs associated with this complication into account nor those related to the decision to terminate or continue the pregnancy after a positive diagnosis. In addition to total costs and cost per case diagnosed, we calculated the number of amniocenteses and the rate of iatrogenic fetal loss per DS case diagnosed for each approach. Table 12 summarizes the parameters used in the analysis, with the baseline estimates and the variations considered in the sensitivity analyses.

Appendix D presents, in detail, the baseline parameters and the estimates used in the sensitivity analysis regarding the incidence of Down syndrome in the Quebec population, as well as the effectiveness of screening and diagnosis. The detection rate and number of cases diagnosed uses a 23% rate of spontaneous loss of DS fetuses between second trimester and term.

6.3 Cost breakdown of the various approaches

All of the direct costs associated with screening and diagnostic procedures are considered. Details of the calculations and the source of these costs are given in Appendix E. Table 13 summarizes costs considered in the base case scenario, as well as the probability intervals used in the sensitivity analyses.

6.4 Cost effectiveness analysis of the selected approaches

We analyzed the costs and effectiveness of screening/diagnosis for DS using the approaches presented in Table 11. These represent the strategies that we consider to be the most appropriate; however, they could be modified or other approaches could be added to the list. The birth data correspond to birth projections for Quebec in the year 2000 [61], and the results presented apply

specifically to this year. It should be noted that the birth curve based on maternal age shifts slowly such that, while the number of births after age 30 increases yearly, the total number of births gradually declines (see Appendix A).

6.4.1 Base case scenario

Table 14 summarizes the results obtained when calculating the costs and effectiveness of the selected approaches, using the baseline parameters presented in Tables 12 and 13.

Approach #1 (amnio 35 +) represents the current practice in Quebec. Screening is based on maternal age, and amniocentesis is offered to pregnant women aged 35 and over at time of delivery. Given these conditions and the fact that 60% of women currently proceed to diagnosis, 5,458 amniocenteses would be performed in the year 2000 in Quebec, in order to diagnose 28 cases of Down syndrome (36 cases would be diagnosed if the risk at second trimester is considered rather than the risk at term). One hundred and ninety-seven amniocenteses would have to be performed for each case diagnosed. There would be 27 cases of iatrogenic fetal loss, for a fetal loss/case diagnosed ratio of 0.98; this means there would be almost as many cases diagnosed as iatrogenic fetal losses. The cost per case diagnosed would be $97,965, assuming genetic counselling fees of $29.30 per visit, or the same as the cost of a medical visit. If total genetic counselling fees were $77.40, the total impact of visit costs would be $422,418 instead of $159,908; total cost per year would come to $2,978,103 and the cost per case diagnosed would be $107,435 (an additional $9,470).

Approach #2 (universal MSS) considers the possibility of providing MSS to all pregnant women, regardless of their age: amniocentesis would only be offered when screening identified a high risk. In this situation and taking the base case parameters into consideration, 34 cases of DS would be diagnosed by performing 2,843 amniocenteses, or 84 amniocenteses per case diagnosed. The number of spontaneous fetal losses following amniocentesis would be considerably lower (14 cases), giving a ratio of fetal loss/case diagnosed equal to 0.42. The total cost per year is comparable to that of approach #1, with a cost of $81,713 per case diagnosed.

Approach #3 (universal MSS, amnio 35 +) offers MSS to all women under 35, and a choice of MSS or amniocentesis for those 35 and over. This approach represents the current program of maternal serum screening in Ontario. Although the number of amniocenteses performed is higher than the current number in Quebec, this approach would permit the diagnosis of 51 cases of DS and would result in 32 cases of iatrogenic fetal loss. If the decision were made to offer MSS to women under 35 and retain amniocentesis for those 35 and over, one would be looking at approach #4 (MSS < 35, amnio 35 +). The number of amniocenteses and the cost of the program would be twice as high as for the current approach (#1), but the number of cases diagnosed would also be doubled, while maintaining an iatrogenic fetal loss/case diagnosed ratio of less than 1.

At age 37, a pregnant woman has a 1:242 risk of having a child affected with DS. Several studies consider 1:250 as the high-risk threshold. Approaches #5 (universal MSS, amnio 37 +) and #6 (MSS < 37, amnio 37 +) are similar to #3 and #4 above, but the cutoff age for MSS or amniocentesis is 37 years. Both strategies present a higher total cost than the current approach, but performance is better. As many as 46 or 52 cases would be diagnosed, depending on whether the women aged 37 and over had the option of MSS screening.

An ultrasound examination enables confirmation of the gestational age and diagnosis of multiple pregnancies and certain malformations. In the base

Table 14: Detailed cost-effectiveness analysis results for each approach considered, according to the parameters estimated in the base case scenario

	1 Amnio 35 +	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS <35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS <37 Amnio 37 +
No. of serum tests	0	41,251	41,251	36,248	41,251	38,774
No. of ultrasounds	0	3,345	3,345	2,926	3,345	3,134
No. of amniocenteses	5,458	2,843	6,323	10,219	4,566	6,491
Cost of serum tests	0	$1,079,129	$1,079,129	$948,256	$1,079,129	$1,014,340
Cost of ultrasounds	0	$83,631	$83,631	$73,155	$83,631	$78,340
Cost of amniocenteses	$2,555,685	$1,331,529	$2,960,779	$4,785,292	$2,138,094	$3,039,665
Cost of genetic counselling	$159,908	$258,921	$528,213	$824,914	$392,235	$538,795
Total cost per year	$2,715,593	$2,753,210	$4,651,751	$6,631,616	$3,693,088	$4,671,139
Cost/diagnosed case	**$97,965**	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,218**
Amniocenteses/diagnosed case	**197**	**84**	**123**	**173**	**98**	**125**
DS cases diagnosed	**28**	**34**	**51**	**59**	**46**	**52**
Iatrogenic fetal loss	**27**	**14**	**32**	**51**	**23**	**32**
Fetal loss/diagnosed case	**0.98**	**0.42**	**0.62**	**0.87**	**0.49**	**0.63**

Amnio: Amniocentesis
MSS Maternal serum screening
Note: The number of DS cases diagnosed and iatrogenic fetal losses are estimated. Although these figures have been rounded to the nearest whole unit in the table, the ratios calculated use the actual estimated values.

case scenario, all MSS strategies include an ultrasound for confirmation of the age once screening has detected an elevated risk. This is the current practice in Ontario and is designed to reduce the after positive screening and points out the weak influence that this practice has on the effectiveness of screening. Since there is no consensus on this issue either in practice or in the literature, we have calculated a scenario that inclusdes the routine use of ultrasound prior to screening (detection rate: 67%; false positive rate: 5%). If this scenario is incorporated into the universal MSS approach, the number of amniocenteses is decreased by 37%; the reduction is, however, equally substantial for the

Table 15: Results of the sensitivity analysis, varying the MSS detection rate and prenatal screening/diagnosis participation rates

	No. of DS cases diagnosed	No. Of iatrogenic fetal losses	Cost per case diagnosed ($000)	Total cost ($000,000)
2: Universal MSS				
Base case (maximum, minimum detection)	34 (36, 31)	14 (18, 11)	82 (89, 76)	2.8 (3.2, 2.3)
Base case (maximum, minimum participation)	34 (39, 29)	14 (16, 12)	82 (79, 84)	2.8 (3.1, 2.4)
3: Universal MSS, Amnio 35 +				
Base case (maximum, minimum detection)	51 (53, 48)	32 (35, 28)	91 (95, 88)	4.7 (5.1, 4.2)
Base case (maximum, minimum participation)	51 (56, 47)	32 (33, 30)	91 (88, 93)	4.7 (4.9, 4.4)
4: MSS < 35, Amnio 35 +				
Base case (maximum, minimum detection)	59 (60, 57)	51 (54, 48)	113 (116, 110)	6.6 (7.0, 6.3)
Base case (maximum, minimum participation)	59 (64, 54)	51 (55, 47)	113 (112, 113)	6.6 (7.2, 6.1)
5: Universal MSS, Amnio 37 +				
Base case (maximum, minimum detection)	46 (48, 43)	23 (26, 19)	80 (85, 76)	3.7 (4.1, 3.3)
Base case (maximum, minimum participation)	46 (51, 42)	3 (25, 21)	80 (78, 81)	3.7 (4.0, 3.4)
6: MSS < 37, Amnio 37 +				
Base case (maximum, minimum detection)	52 (53, 50)	32 (36, 29)	90 (95, 86)	4.7 (5.1, 4.3)
Base case (maximum, minimum participation)	52 (57, 47)	32 (36, 29)	90 (89, 91)	4.7 (5.1, 4.2)

other proposed approaches. As many cases of DS would be diagnosed with less iatrogenic fetal loss and an increase in total cost of 5-13% depending on the different approaches (Table F.12, Appendix F).

Base case scenario calculations, using different detection and false positive rates for women under number of false positives and, consequently, to avoid a certain number of amniocenteses. However, the scientific literature discusses the danger

Table 16: Variation in total cost and cost-effectiveness ratio (cost per case diagnosed) for the different proposed approaches (scenarios a, b, c, d)

Approach	Total cost ($000,000)			C/E ratio ($000)			Variation (%)*	
	Base	Max.	Min.	Base	Max.	Min.	Max.	Min.
2: Universal MSS	2.8	4.1	2.5	82	123	74	+51	-9
3: Universal MSS, Amnio 35 +	4.7	6.0	4.2	91	118	82	+30	-9
4: MSS < 35, Amnio 35 +	6.6	7.9	5.9	113	133	101	+18	-11
5: Universal MSS, Amnio 37 +	3.7	5.1	3.4	80	110	73	+38	-8
6: MSS < 37, Amnio 37 +	4.7	6.0	4.2	90	116	82	+28	-9

*Variation between the scenario specified (max. or min.) and the base case scenario, expressed as a %.

of reclassifying cases 35 years and for those 35 years and over (parameters presented in Table 12), show a small decrease in number of diagnosed cases, but a reduction in the number of iatrogenic fetal losses of 13-21%, as well as a reduction of 3-11% in the C/E ratio relative to the base case scenario given in Table 14.

Finally, even though all of the alternative approaches presented demonstrate greater effectiveness than the current situation with respect to the number of cases diagnosed, the number of amniocenteses per case diagnosed and the rate of iatrogenic fetal loss per case diagnosed, not more than about half of expected DS births would be diagnosed under any of the proposed strategies.

6.4.2 Sensitivity analysis

Variation in effectiveness parameters

Five scenarios have been calculated for each proposed approach, based on variation in screening effectiveness parameters (see Table 12):

a) maximum detection rate (69%; 10% false positives)

b) minimum detection rate (59%; 6% false positives)

c) maximum participation rate in screening (60%) and in diagnosis (90%)

d) minimum participation rate in screening (50%) and in diagnosis (80%)

e) iatrogenic fetal loss rate equal to 1%

The results of the sensitivity analysis are given in Table 15.

For all of the approaches analyzed, the number of detected cases is higher under the maximum detection rate scenarios, but the consequent increase in false positives implies a greater number of amniocenteses, with more cases of iatrogenic fetal loss and higher costs. The reverse situation is found under the minimum detection rate scenarios.

In addition, when a greater number of pregnant women participate in screening and diagnosis, the number of diagnosed cases is greater than that obtained by increasing the detection rate of the serum test. Total cost is higher with more participation, although the cost per case detected is lower because of the greater number of cases diagnosed. For all of the approaches analyzed, the effectiveness of DS screening in terms of diagnosed cases and iatrogenic fetal loss per case diagnosed is superior to the current strategy.

However, the number of iatrogenic fetal losses is greater in three of the proposed approaches compared to the current situation. It should be remembered that all of the scenarios use a 0.5% iatrogenic fetal loss rate (i.e. fetal loss related to the amniocentesis procedure). If this rate is increased to 1%, the number of unaffected cases lost following the procedure doubles. This also applies to the current situation.

We have calculated two additional scenarios in order to evaluate the possibility that the best or worst estimates for each parameter occur simultaneously, assuming base case scenario costs and an iatrogenic fetal loss rate of 0.5%. The results suggest that, under the best conditions (highest detection rate, highest participation in screening and diagnosis), as well as in the unlikely case that all parameters are at their lowest value, all of the proposed strategies represent better options than the current approach (see Table F.6, Appendix F).

Appendix F presents detailed sensitivity analysis results for each of the proposed approaches.

6.4.2.2 Variation in costs of procedures

Six scenarios with varying costs associated with screening and diagnostic procedures were calculated, as follows:

a) variation in cost of the genetic counselling visit – i.e. 1½ hours ($116.10), ½ hour ($38.70) or a medical visit instead of genetic counselling ($29.30);
b) variation in MSS cost – i.e. maximum $60, minimum $20;
c) variation in ultrasound cost – i.e. maximum $50, minimum $20;
d) variation in cost of amniocentesis – i.e. maximum $500, minimum $400;
e) maximum cost of all interventions;
f) minimum cost of all interventions.

The sensitivity analysis assumed the screening and diagnosis effectiveness parameters used in the base case scenario. Results are summarized in Table 16.

For all of the approaches analyzed, the total maximum cost and highest C/E ratio correspond to the scenario that assumes a maximum cost for the serum test. The total minimum cost and lowest C/E ratio correspond to the scenario which uses the minimum cost for amniocentesis, except for approach #2 where the cost of the serum test determines the lowest total cost scenario. In the unlikely case that all costs correspond to the maximum values estimated, the total cost of screening and diagnosis would vary from $4.5 million (universal MSS) to $8.7 million (MSS <35, amnio 35+). The cost per case of DS diagnosed (C/E ratio) would be $133,137 and $147,600, respectively, for the same approaches. At the other extreme, in the equally unlikely case that all costs correspond to their lowest estimates, the total cost would vary from $2.1 million (universal MSS) to $5.2 million (MSS <35, amnio 35+). The estimated C/E ratio would be $63,137 and $78,965 for the same two approaches (see Table F.11, Appendix F).

Appendix F presents detailed sensitivity analysis tables with varying costs for the different parameters.

6.5 Discussion of results

In the preceding analysis, we considered various prenatal screening and diagnostic approaches and evaluated the impact of each approach on the number of DS cases diagnosed, the number of cases of iatrogenic fetal loss, the cost-effectiveness ratio (defined as the cost per case of DS diagnosed) and the total cost of the program. We have compared the results of the various approaches to the current prenatal diagnosis program in Quebec.

The results suggest that the present program, which offers amniocentesis to women who are 35 years and over at the time of delivery, is relatively expensive with low performance. All of the other approaches evaluated would be more effective, in detecting more cases with a better rate of iatrogenic fetal loss per case diagnosed. The proposed approaches involve a higher total annual cost than that currently incurred, but the cost per case is generally lower because of better performance with respect to the number of cases diagnosed.

The approaches that provide a better detection rate also involve a greater number of amniocenteses and, consequently, a greater number of cases of iatrogenic fetal loss. Access to MSS for all pregnant women, regardless of age (approach #2: universal MSS and amniocentesis for high-risk cases only), seems to provide a good detection rate and the least impact on the iatrogenic effects associated with screening. The absolute number of iatrogenic fetal losses is the lowest (14), as is the fetal loss/case diagnosed ratio (0.42). A similar approach was presented as one of the options in a recently published decision analysis [114]. The detection rate for that approach was estimated at 44% in the base case scenario, compared to 31% (34 cases in 111) in the present study. The disparity may be due to the use of different parameter estimates, notably a screening participation rate of 80%. If more pregnant women participate in screening, it follows that a greater number of cases will be detected, with an increase in total cost and a reduction in cost per diagnosed case.

Assuming a 100% participation rate for both screening and diagnosis, we obtained a detection rate of 65% (72/111) for approach #2, with 8% false positives, compared to a detection rate of 54% (60/111) and 12% false positives for approach #1. These results are comparable to those reported by Seror and Costet, who also stressed the importance of values with respect to DS and pregnancy loss in the decision-making process [113]. Independent of its effectiveness in terms of diagnosed cases and iatrogenic fetal loss, approach #2 implies the loss of a current right – i.e. access to amniocentesis for women 35 years and over, without prior screening.

Current rights would be maintained in an approach which offers MSS to all women but which makes amniocentesis without prior screening available to women 35 years of age and over who wish it (approach #3: universal MSS, amnio 35+). The total cost for this approach is approximately 43% higher than that for the current strategy. With a view to improved performance, however, the cost-effectiveness ratio would be 18% lower than at present. Almost half the number of DS cases expected (51/111) would be diagnosed, with a fetal loss per case diagnosed ratio of 0.62.

Results for the same approach with an age cutoff of 37 years for the choice of amniocentesis or MSS (approach #5) are comparable, with fewer amniocenteses performed, less iatrogenic fetal loss and lower cost. This approach is worth considering, although it runs counter to current practice in Quebec by delaying the eligibility for amniocentesis without prior screening by two years.

The variation in the cost of MSS has the greatest impact. We calculated a maximum cost of $60, which may be too high. However, this takes the opinion of Quebec professionals into account and

is a feasible estimate, because the initial cost of MSS at the start of the Ontario screening program was $86. Using ultrasound prior to MSS for all women screened increases the total cost of the program by 5-13% compared to the base case scenarios. Ultrasonography also improves screening efficacy. However, between 36,000 and 41,000 ultrasound examinations would have to be performed, whereas about 3,000 would be carried out under the base case scenarios.

The preceding analysis shows that, in terms of diagnostic performance and cost-effectiveness, there are advantages in offering MSS to all pregnant women. The ethical considerations surrounding DS screening and diagnosis cannot be disregarded when selecting one approach over another. Introducing serum marker screening enables the prenatal diagnosis of a greater number of DS cases, but each approach leads to the loss of unaffected fetuses as a result of amniocentesis. The three universal MSS approaches do not seem to have a major impact on the total cost of screening and their cost effectiveness ratios are superior to that in the current situation. Thebest strategy is that which makes maternal serum screening available to all pregnant women, maximizes the detection rate and minimizes iatrogenic fetal loss, permits the voluntary, informed participation of women, and preserves existing rights, notably the right to amniocentesis as of age 35 in Quebec.

7. ORGANIZATION OF A DOWN SYNDROME SCREENING STRATEGY FOR QUEBEC

This section focuses on several important points concerning the availability and organization of resources in order to make DS screening accessible in Quebec. The Ontario experience can be used to guide the organization and management of screening-related services. In Ontario, a provincial coordination committee and several subcommittees are responsible for training professionals and monitoring medical practice, genetic counselling and the laboratories.

The training of health care professionals responsible for genetic counselling is an essential feature. Those responsible for prenatal care will have to provide their patients with information about the availability of MSS, its implications and consequences, as well as the basics of interpreting results based on an estimation of risk. The number of pregnant women referred to screening and diagnostic services has a strong influence on the extent to which such women participate in screening. If screening indicates a high risk, rapid communication will be required to inform the pregnant woman, make an appointment for specialized genetic counselling and ultrasound confirmation of the gestational age (when possible under the program) and alert the cytogenetics laboratory. At this point, pregnant women are generally in their second trimester and have little time to make decisions.

Serum screening should be limited to certain laboratories in the province, in order to ensure the quality of screening at the laboratory level [121]. Screening requires the prior determination of the median values of the various serum markers in the population; uniform, standardized protocols to evaluate individual risk levels; uniform methods for selecting screening kits in all laboratories; and the establishment of forms for collecting sociodemographic data and information on other important screening variables. Quality control at the laboratory level is of vital importance, particularly considering the rapid advances being made in this field, and the advent of new markers, technologies and equipment.

Access to serum screening will require the establishment of norms specific to the Quebec population for the calculation of risk. To offset variations inherent to each individual, to measurement method and to related variables, marker measurement is expressed in multiples of the median (MoM); data on the local population are therefore required to establish the medians that will serve as a basis for later comparison. This stage will take several months.

Once this experimental phase ends, Quebec laboratories would be able to carry out large-scale tests. These would require simple, automated procedures. One of the most complex aspects is the interpretation of the results and estimation of risk, which may require special training for the laboratory personnel. Even if software is available to carry out this work, professional interpretation remains essential. Regular adjustments will have to be made to standardize measurements and verify the false negative and false positive rates, modifying the risk cutoff point if necessary.

A major limitation with respect to generalizing screening is the capacity to perform amniocenteses. Based on this study, it seems that the number of diagnosed cases can be augmented by reducing or slightly increasing the number of amniocenteses. However, even with a decrease in the number of amniocenteses, the methods of operation of the cytogenetics laboratories could be affected. Serum screening followed by ultrasound to confirm the date and by a genetic counselling visit may result in substantial delays. Cytogenetic tech-

niques and karyotype studies require an average of 14 days before a final report can be produced (personal communication, Dr. A. Duncan, Cytogenetics Laboratory, Montreal Children's Hospital), but this delay can vary depending on the particular centre.

The Royal Commission on New Reproductive Technologies estimates that it usually takes two to four weeks for amniocentesis results to be obtained [110]. This represents the time for the attending physician to receive the results, and it could be even longer before the woman is informed; the delays are generally shorter if the result is abnormal. To avoid lengthy delays, cytogenetics laboratories – whose workload may increase, decrease or stay the same over time – may require additional personnel in order to minimize the waiting time for results.

Whenever serum screening indicates an elevated risk, specialized genetic counselling must be offered to pregnant women or to couples to inform them about the interpretation of the risk, the possibility of amniocentesis and the risks inherent to this procedure, as well as the clinical and genetic aspects of DS. A genetic counselling visit in Canada lasts an average of one hour [110]. There are five genetic counsellors in practice in Quebec, only one of whom works exclusively in prenatal counselling. There are 34 in Ontario, 25 in Alberta and 10 in British Columbia. In the rest of the Canadian provinces, the number varies from one to four. Paradoxically, McGill University in Montreal is one of the two Canadian universities – the other being University of British Columbia – that offers a Master's degree in genetic counselling and its graduates rapidly find employment in other Canadian provinces (information provided in June 1998 by Dr. A. Duncan, Director, Cytogenetics Laboratory, Montreal Children's Hospital).

Our analysis does not take into account the cost of putting screening facilities in place. This may be negligible when spread out over the number of pregnancies. At the biochemistry laboratory level, the present serum tests do not involve any technological additions, and the supervision and interpretation of results could be carried out by a few extra people. The establishment of committees, if needed, will require the involvement of health care professionals, who should participate on a voluntary, committed basis; the associated costs have not, however, been calculated.

8. CONCLUSION

Down syndrome is the most common of the severe chromosomal abnormalities. Its incidence in the population is 1 for every 700 to 1,000 births, and varies depending on the mother's age, increasing as the mother's age at time of delivery rises. In Quebec, the prenatal diagnosis of DS is currently performed by amniocentesis during the second trimester, which is offered to all pregnant women aged 35 and over at the time of delivery. The public health care system makes no provision for diagnosis for younger women, who account for more than half of DS births. In addition, new non-invasive prenatal screening techniques have been developed in the past few years. Maternal serum markers, for example, widen the audience for screening to include younger women, and better target women at risk in order to limit the number of amniocenteses and their associated complications, the most serious of which is the loss of an unaffected fetus. Other screening and diagnostic techniques are now being studied; some of them are already in use, although there is no consensus in the scientific literature as to their use and performance.

Serum markers would provide a detection rate of 65%. However, about 8% of the women screened will be considered at high risk on testing, even though the fetus is, in fact, unaffected – i.e. a false positive result. There will also be a proportion of cases where the fetus is affected and screening will not detect the abnormality. In such cases, parents may feel reassured during the pregnancy but will have to face a diagnosis of DS at the birth. Understanding that screening is based on the concept of risk is therefore of critical importance. This means that elevated risk is not diagnostic of DS, and that low risk is not confirmation of an unaffected fetus. To date in Quebec, the only definitive confirmation of a DS diagnosis during pregnancy comes from a karyotype study of fetal cells obtained by amniocentesis. Of all the diagnostic techniques studied in this report, second-trimester amniocentesis represents the best choice, taking into account the risks associated with the procedure and its availability in Quebec.

Prenatal screening using serum markers estimates the individual risk for each pregnancy and, in all cases where the risk is considered high, amniocentesis is recommended to confirm the diagnosis. We have considered six approaches in this report that define different ways to make MSS screening available. We have examined the performance of each approach in the population of pregnant women expected in Quebec in the year 2000. The evaluation criteria were the number of cases of DS diagnosed, the number of cases of fetal loss due to amniocentesis and the rate of fetal loss per case diagnosed. The cost per case diagnosed (cost-effectiveness ratio) was also analyzed, together with the total annual cost of providing a screening strategy under various scenarios.

The *Conseil* believes that there are benefits to introducing MSS for Down syndrome. Several approaches and scenarios have been analyzed, and all have been shown to be more effective than amniocentesis for women 35 years of age and over. Of the five alternative approaches examined, it appears that the most beneficial would be that whereby MSS is offered to all pregnant women, with amniocentesis available in high-risk cases after screening, or without prior screening for women aged 35 and over (or age 37 and over) if they so desired. The age cutoff at 35 or 37 years provides a better detection rate, but at a higher total cost than for the current program. Amniocentesis for women 35 years and over has become the norm for pregnant women and, given the anxiety that their pregnancy may generate because of the increased risk of chromosomal malformations, it may be difficult to cease to offer the choice of amniocentesis to these women. However, pregnant women may prefer to choose se-

rum screening if they have been well-informed of the risks associ-

ated with amniocentesis. Voluntary participation of women and genetic counselling are essential if they are to understand the benefits and limitations of screening, and thus be able to make an informed decision.

The following findings result from this evaluation, which has been carried out with an in-depth examination of the relevant literature and a cost-effectiveness analysis adapted to the Quebec situation:

Screening

- There is sufficient evidence to recognize maternal serum marker screening as a technique suitable for generalized use in the population, provided that the quality of services offered is ensured and that participation is on a voluntary, informed basis.

- With respect to the importance of genetic counselling, particular attention should be paid to the training of professionals and the allocation of resources to this area of clinical practice.

- Training should be given to professionals offering first-line genetic counselling and those providing specialized counselling.

- The present evaluation is based on triple-marker data, but the same principle can be applied to the combination of two or even four markers.

- First-trimester markers offer numerous possibilities, but there is as yet no consensus in the literature regarding their use and effectiveness. Screening during the first trimester would result in amniocentesis being performed on a certain number of DS fetuses that would have aborted spontaneously between the first trimester and term.

- The use of ultrasonography in screening and diagnosis is promising, but there is no consensus on its performance at present. In addition, its use for the screening and diagnosis of DS requires more sophisticated technology than routine obstetric ultrasound, as well as proper technician training.

Diagnosis

- Chorionic villus sampling allows earlier diagnosis than second-trimester amniocentesis, but carries a greater risk of false positive results and complications, particularly fetal loss. In addition, the procedure is more difficult to perform, and its use in Quebec is very limited.

- Amniocentesis during the first trimester would also permit earlier diagnosis, but presents higher risk for the fetus.

- New, non-invasive techniques are now being studied, such as the identification of fetal cells in maternal blood. If costs prove reasonable, these techniques would open up an avenue worth exploring.

- Second-trimester amniocentesis remains the best technique, and it is currently available in Quebec. Its limitations are essentially the risk of fetal loss (estimated at 0.5% in Quebec) and the inevitable delay that means diagnosis is made fairly late in the pregnancy.

Results

- Prenatal screening for DS using maternal serum markers, regardless of the scenario and cost parameters used, represents an advantageous option compared to the current situation.

- Based on birth projections for Quebec in the year 2000, MSS would enable the diagnosis of 34 to 59 of the 111 DS cases expected, us-

ing base case scenario parameters and according to the different proposed approaches, compared to 28 for the current situation.

- The iatrogenic fetal loss/case diagnosed ratio is between 0.42 and 0.87 depending on the approach, versus 0.98 for the current situation.

- The cost-effectiveness ratio (cost per case of DS diagnosed) varies from $81,713 to $112,544 depending on the approach, versus $97,965 for the current situation.

- The total annual cost of a DS screening and diagnostic strategy varies between $2.8 million and $6.6 million.

- Considering the number of cases diagnosed, iatrogenic fetal loss, total annual costs and cost per case diagnosed, the most advantageous strategy appears to be offering MSS to all pregnant women, with the choice of either MSS or amniocentesis for women 37 and over. On the other hand, if the choice could be offered as of 35 years of age, the approach would prove to be slightly more expensive but would be fairer. In fact, this is the only approach that allows universal access to screening, while retaining the right to amniocentesis without prior screening for women 35 years and over.

To conclude:

- *The Conseil considers that prenatal screening for Down syndrome using maternal serum markers should be made available to all pregnant women in Quebec, regardless of age.*

- *The participation of pregnant women in screening must be voluntary and based on informed choice, relying on complete, high quality information provided by first-line health care professionals (physicians, nurses, midwives, etc.) who are familiar with prenatal screening and its benefits and limitations (false positive and false negative results).*

- *A woman's decision to undergo amniocentesis once prenatal screening indicates a high risk of Down syndrome or another chromosomal abnormality must also be voluntary and based on informed choice, relying on complete, high quality information provided by professionals trained in genetic counselling.*

- *The best screening strategy is one that permits more cases of Down syndrome to be diagnosed with the lowest risk of iatrogenic fetal loss at an acceptable cost. The selection of an age cutoff point for amniocentesis without prior screening should take existing rights into account, as well as the anxiety brought about by the possibility of having a child with Down syndrome for women aged 35 years and over.*

- *The screening and diagnostic strategy adopted for Down syndrome must be flexible, so that it can adjust rapidly to new technological developments.*

APPENDIX A:
INCIDENCE OF DOWN SYNDROME IN THE QUEBEC POPULATION AND RISK DISTRIBUTION BASED ON MATERNAL AGE

Table A.1: Expected births in Quebec in 2000, based on maternal age and risk of Down syndrome (DS)*

Maternal age	Number of Births	According to Bray et al. [16]		According to Cuckle et al. [34]	
	Quebec 2000	DS risk	Expected cases	DS risk	Expected cases
13-14	34				
15	107	1:1493	0.1	1:1578	0.1
16	269	1:1493	0.2	1:1572	0.2
17	531	1:1486	0.4	1:1565	0.3
18	1060	1:1476	0.7	1:1556	0.7
19	1764	1:1462	1.2	1:1544	1.1
			Total: 2.5 (2.1 %)		Total: 2.4 (2.2 %)
20	2336	1:1445	1.6	1:1528	1.5
21	2759	1:1423	1.9	1:1507	1.8
22	3245	1:1395	2.3	1:1481	2.2
23	3783	1:1359	2.8	1:1447	2.6
24	4480	1:1315	3.4	1:1404	3.2
			Total: 12.1 (9.8 %)		Total: 11.4 (10.2 %)
25	4862	1:1259	3.9	1:1351	3.6
26	5050	1:1193	4.2	1:1286	3.9
27	5262	1:1115	4.7	1:1208	4.4
28	5323	1:1025	5.2	1:1119	4.8
29	5271	1:926	5.7	1:1018	5.2
			Total: 23.7 (19.2 %)		Total: 21.8 (19.7 %)
30	5039	1:821	6.1	1:909	5.5
31	4484	1:714	6.3	1:796	5.6
32	3823	1:608	6.3	1:683	5.6
33	3415	1:508	6.7	1:574	5.9
34	3009	1:416	7.2	1:474	6.3
			Total: 32.7 (26.5 %)		Total: 29.1 (26.2 %)
35	2567	1:336	7.6	1:384	6.7
36	2026	1:268	7.6	1:307	6.6
37	1512	1:211	7.2	1:242	6.2
38	1042	1:164	6.4	1:189	5.5
39	760	1:127	6.0	1:146	5.2
			Total: 34.7 (28.2 %)		Total: 30.3 (27.3 %)
40	495	1:97	5.1	1:112	4.4
41	318	1:75	4.2	1:85	3.7
42	195	1:57	3.4	1:65	3.0
43	100	1:43	2.3	1:49	2.0
44	45	1:33	1.4	1:37	1.2
			Total: 16.5 (13.5 %)		Total: 14.3 (12.9 %)
45	23	1:25	0.9	1:28	0.8
46	6	1:19	0.3	1:21	0.3
47	4	1:14	0.3	1:15	0.3
48	3	1:11	0.3	1:11	0.3
			Total: 1.8 (1.4 %)		Total: 1.7 (1.5 %)
Total	75002	1:608	124 cases	1:675	111 cases

* Birth data by age group supplied by ISQ, June 1999, *Perspectives de la population du Québec, 1996-2051* [62]

Table A.2: Percentage (%) of births by age group and year in Quebec, for 1991, 1993, 1995, 1996 and projection for 2000

Age	1991	1993	1995	1996	2000
15-19	4.1	4.42	4.70	4.72	4.97
20-24	20.4	19.37	19.39	19.63	22.14
25-29	41.0	37.96	34.72	34.29	34.36
30-34	26.5	28.73	30.06	29.42	26.36
35-39	7.1	8.39	9.72	10.49	10.54
40-44	0.9	1.11	1.33	1.38	1.54
45-49	N/A*	0.02	0.04	0.05	0.05
	100.00	100.00	100.00	100.00	100.00

* N/A: Not available

Sources: Statistics Canada (Demographics Division), Population Estimates, and *Bureau de la statistique du Québec*, Update March 7, 1997 [120].

ISQ 1999, *Perspectives de la population du Québec, 1996-2051* (unpublished data) [61]

Table A.3: Incidence of Down syndrome (DS) and number of cases diagnosed for Quebec and Canada, 1992-1997

Year	Quebec			Canada		
	DS Newborns	DS fetuses (%)*	Total	DS Newborns	DS fetuses (%)*	Total
1992	97	43 (31)	140	415	285 (41)	700
1993	68	55 (45)	123	391	300 (43)	691
1994	59	66 (53)	125	386	300 (44)	686
1995	106	51 (32)	157	451	336 (43)	787
1996	89	59 (39)	146	394	395 (50)	789
1997	76	67 (47)	143	412	395 (49)	807

*Cytogenetically diagnosed cases of DS, using amniotic fluid, chorionic villus or fetal blood cell sampling, and percentage (%) of fetuses diagnosed out of the total number of cases expected at birth

APPENDIX B:
DESCRIPTION OF SCREENING AND DIAGNOSTIC METHODS FOR DOWN SYNDROME

APPENDIX B: DESCRIPTION OF SCREENING AND DIAGNOSTIC METHODS FOR DOWN SYNDROME

Serum markers

AFP is a protein produced by the yolk sac, fetal gastrointestinal tract and fetal liver [96]. AFP is present in the maternal circulation through diffusion across the placenta and amnion. For unknown reasons, maternal AFP serum level continues to rise until the 28th to 32nd weeks of gestation, long after reaching its maximum in fetal plasma and amniotic fluid [96]. AFP is the second most important protein in the fetal circulation, after albumin. It achieves its maximum concentration in fetal plasma around the 12th to 15th week of gestation. AFP is also found in amniotic fluid and maternal serum, as it crosses the placental barrier. Concentration in maternal serum increases from the 13th week of pregnancy to the 32nd, at which point it gradually diminishes. The increase is delayed in women with diabetes [28].

Estriol is a steroid hormone produced by the syncytiotrophoblast, the outermost part of the placenta in direct contact with the maternal circulation [96]. Its unconjugated form is a placental product derived from precursors in the fetal liver and adrenal gland [78].

hCG is a glycoprotein secreted by the syncytiotrophoblast, and is composed of two covalently bound subunits, α and β. Over 99% of hCG circulates in the blood intact.

Inhibin is a glycoprotein hormone secreted in multiple forms, including as an alpha subunit and as two heterodimers: alpha/beta-A (inhibin A) and alpha/beta-B (inhibin B). Total inhibin includes inhibin A, inhibin B and the α subunits. In early pregnancy, inhibin is secreted from both the corpus luteum and the placenta, with the latter becoming the major source after the first trimester. Its function during pregnancy is unknown [136].

Ultrasonography (Ultrasound)

Ultrasound as a prenatal screening method is currently under development in a number of research centres throughout the world. The technique is already used for a broad range of obstetric indications, such as estimating gestational age, monitoring fetal growth, detecting fetal abnormalities and guiding amniocentesis and chorionic villus sampling. The ultrasound technique consists of placing a transducer on the abdomen, which transmits sound waves that reflect off the fetus, producing images that can be viewed and analyzed. Prenatal exposure to ultrasound is considered safe, based on epidemiological studies [111]. More sophisticated forms of the technique, such as transvaginal ultrasonography, colour flow imaging and Doppler ultrasonography are now available.

The use of ultrasound for screening purposes requires that the results be valid and reliable, and that its application be standardized across centres that have varying degrees of expertise and equipment. The result partially depends on the training and skill of the operator.

Amniocentesis

Amniocentesis is an outpatient procedure usually performed between the 14th and 16th week of pregnancy. It is preceded by an ultrasound examination to confirm the week of gestation, determine the number and viability of fetuses, locate the placenta and puncture site, and estimate amniotic fluid volume [41]. Using ultrasound guidance, a needle is inserted through the abdomen into the uterine cavity, and 20-30 mL of amniotic fluid containing maternal and fetal cells are aspirated. After amniotic fluid is extracted, the fetal cells are cultured for slightly more than one week in order to allow multiplication. Culturing the fetal cells takes a certain amount of time because

they have been shed and the sample generally contains only a small percentage of cells that are living or active [48].

Once sufficient cells have been obtained, they are treated chemically to stop the division process, so that individual chromosomes can be observed. The chromosomes are then stained, spread out and photographed under the microscope. To ensure that the cells being studied are fetal and not maternal, and also to detect mosaicisms, several cells from different cultures are studied and at least two are fully karyotyped.

A typical karyotype presents the chromosome pairs, arranged according to size. Additional, missing or translocated chromosomes can then be clearly identified. Characteristic banding patterns caused by staining can be used to identify other anomalies [85].

In addition to cytogenetic analysis, fluid and cells collected during amniocentesis can be used for biochemical tests (e.g. using AFP levels to diagnose neural tube defects). However, the main application is the diagnosis of trisomy 21 by karyotyping.

Chorionic villus sampling

Chorionic villus sampling (CVS) is an outpatient procedure performed between the 9th and 12th week of gestation [62]. Two approaches can be used: the transcervical (a catheter is inserted through the vagina), or the transabdominal (with the aid of a needle). Ultrasound helps guide either approach. It is common for two or three attempts to have to be made before sufficient tissue is obtained. CVS does not involve direct analysis of fetal cells, but those from the vascularized projections in the placenta surrounding the fetus. Placental cells differentiate very early in pregnancy from the cells that will become the fetus. Both originate from the fertilized ovum, so their genetic makeup is the same. In 1% of cases, placental cells may in fact differ from fetal cells because of mutations that occur after differentiation of the trophoblast (which gives rise to the placenta) and the fetus. This has obvious implications for the diagnostic accuracy of CVS [62].

Chorionic villi consist of well-differentiated tissues with various types of cells that have specific growth characteristics. Fast-growing cytotrophoblast cells can often be prepared and karyotyped just a few hours after sample collection because they are already dividing. Mesenchymal cells can be cultured in five to eight days, like the cells in the amniotic fluid. Genetic and biochemical tests for the detection of specific conditions can also be carried out on chorionic villus cells.

Fetal cells in maternal blood

As of the first trimester, and as the fetus develops, a small number of fetal cells (trophoblast cells, lymphocytes, granulocytes, nucleated erythrocytes and platelets) detach and make their way into the maternal bloodstream [13]. Platelets have no nucleus and therefore cannot be used for genetic diagnosis. Trophoblast cells have two main disadvantages: (1) approximately 1% of the cells are genetically different from those of the fetus, and (2) a good number have more than one nucleus. Lymphocytes remain in the maternal circulation for long periods, such that it is possible to find them during subsequent pregnancies. Granulocytes have not been studied extensively. Nucleated erythrocytes are the most promising cells for prenatal diagnosis and have been the most widely studied [13]. They have a single nucleus, a limited lifespan and are plentiful during the first trimester of fetal life. Erythrocytes normally have no nucleus when in the adult stage, which could facilitate differentiation of fetal and maternal cells. This point is controversial, because a small number of nucleated maternal erythrocytes can be found in the mother's bloodstream. The major technical difficulty with fetal erythrocytes lies in collecting enough of them for testing. Their con-

centration in maternal blood increases with gestational age. Estimates of concentration vary from 1 fetal cell per 100,000 maternal cells (1 in 10^5) to 1 per billion (1 in 10^9) [13]. There are two ways to "enrich" fetal cell samples: cell sorting and cell concentrating.

This technique is still under development and results are expected in the next few years. At least one study is now ongoing in Quebec.

APPENDIX C:
VARIABLES INFLUENCING SERUM MARKER MEASUREMENT

Table C.1: Variables influencing serum marker measurement

Variables	Effects [141, 144]
Gestational age	The effect is greater for markers whose levels vary significantly with gestational age, e.g. uE3.
Maternal weight	On average, for each 20 kg increase in weight, marker levels decrease by 17% (AFP), 7% (uE3) and 16% (hCG).
Presence of insulindependent diabetes	Marker levels decrease by 10% (AFP), 7% (uE3) and 11% (hCG), after adjustment for maternal weight.
Ethnic origin	AFP and hCG levels are slightly higher in black women (15 and 18%, respectively, after adjustment for maternal weight). Levels of uE3 and hCG are higher in women from South Asia (7 and 6%, respectively).
Smoking during pregnancy	On average, hCG levels in female smokers are 18% lower than in non-smokers. There is very little effect with respect to the other markers. No adjustment is generally made for this variable.
Consecutive pregnancies	There seems to be a negative correlation between HcG level and parity. The effect on detection rate is 0.1%. No adjustment is generally made for this variable.
Multiple pregnancies	Marker levels are almost doubled. Even taking this into consideration, the problem remains that one of the fetuses may be affected. Screening is not indicated in multiple pregnancies.

APPENDIX D: ESTIMATION OF PARAMETERS USED IN THE COST-EFFECTIVENESS ANALYSIS OF SCREENING AND DIAGNOSTIC STRATEGIES FOR DOWN SYNDROME

APPENDIX D: ESTIMATION OF PARAMETERS USED IN THE COST-EFFECTIVENESS ANALYSIS OF SCREENING AND DIAGNOSTIC STRATEGIES FOR DOWN SYNDROME

Number of births

The total number of births in Quebec and their distribution based on maternal age are well known. The analysis uses birth projections for Quebec for the year 2000. A total of 75,002 births is expected for year 2000, 12% of which will be to mothers aged 35 and over (Appendix A).

Incidence of DS

We applied the risk calculated by Cuckle and Wald [34] for each age bracket to the birth distribution (based on mother's age) expected for Quebec in 2000. On this basis, we estimated the expected number of DS cases at birth to be 111, with 26.2% of these to mothers 30-34 years of age and 14.5% to women 35 and over at the time of delivery (Appendix A). According to the Canadian Cytogenetic Registry, 59 cases of DS were diagnosed in Quebec in 1996 and 89 affected infants were born. Some of the 89 may have been diagnosed prenatally. Assuming that 14 of the 59 DS fetuses diagnosed during the second trimester (23%) would not have reached term, 134 cases would be expected in Quebec. There were 85,250 births in 1996 (Appendix A).

DETECTION AND FALSE POSITIVE RATES

On the basis of the results of four studies (two of which were meta-analyses) and the Ontario maternal serum screening program, we used a detection rate of 65% and a false positive rate of 8% for pregnant women overall. The detection rate varies between 59% (false positive rate = 6%) and 69% (false positive rate = 10%). We also calculated a scenario using the detection rate obtained by Haddow and Palomaki for women under 35 years and for those 35 and over. Table D.1 summarizes the detection rates used in the analysis, which were the most accurate estimates available.

Ultrasonography

Ultrasonography is used to verify the week of gestation when undertaking triple-marker screening, and can also be used alone in DS screening and diagnosis. As far as date estimation is concerned, it can be used for all women before screening, or for those considered at risk after screening. Ultrasound date verification before screening increases the detection rate of serum markers. Under this scenario and taking the results of Wald et al. [134] into consideration, we estimated a detection rate of 67% and a false positive rate of 5% (Table 4). The effect of ultrasound on the detection rate remains questionable, though, if it is only used for cases considered at high risk after screening.

SCREENING PARTICIPATION RATE

There are no Quebec data on the rate of participation in prenatal screening. The overall participation rate in serum marker screening varies from 50 to 55% in Ontario and is approximately 60% in Manitoba. We used a rate of 55% (varying between 50 and 60%).

Diagnosis participation rate

The Royal Commission on New Reproductive Technologies has estimated that 79% of women who are offered amniocentesis agree to it. In Quebec, 7,224 amniocenteses were performed in

Appendix D: Estimation of Parameters used in the Cost-Effectiveness analysis of Screening and Diagnostic Strategies for Down Syndrome

Appendix D: Estimation of Parameters Used in the Cost-Effectiveness Analysis of Screening and Diagnostic Strategies for Down Syndrome

Table D.1: Maternal serum screening detection rate (DR) and false positive rate (FPR)

	Under 35		35 and over		All women	
	DR	FPR	DR	FPR	DR	FPR
Haddow and Palomaki (1993)[1] [52]	48 %	3.7 %	87 %	23 %		
Palomaki et al. (1996) [101]					63 %	5 %
Wald et al. (1997) [141]						
Gestational age using date					64 %	7.5 %
Gestational age using ultra Sound					64 %	5.7 %
Estrada et al. (1998)[2] [43]					64 % (59-69)	8 % (6-10)
Ontario MSSP (1998)[3] [97]					66 %	6 %

[1] Risk cutoff: 1:250
[2] Risk cutoff of 1:195 to 1:380 in the 10 studies included in the meta-analysis
[3] Ontario maternal serum screening program; risk cutoff 1:384

1996 and, in 80% of these (5,779 amniocenteses), the indication was advanced maternal age. There were 10,178 births to mothers aged 35 years and over in that same year, meaning that about 60% of them participated in prenatal diagnosis using amniocentesis. However, no figures are available for the proportion of pregnant women aged 35 and over in Quebec to whom amniocentesis was suggested and, in this analysis, we used the participation rate for the Ontario experience – i.e. 85% for all women, 80% for women 35 and over, and 89% for those under age 35. The diagnosis participation rate used for the current situation was 60%.

IATROGENIC FETAL LOSS

Iatrogenic fetal loss following diagnostic procedures is an undesirable consequence of prenatal screening. The literature cites rates between 0.5 and 2%. In Quebec, consulted practitioners estimated the rate to be 0.5% when amniocentesis is performed around the 16th to 18th week. A scenario was calculated using a rate of 1%.

APPENDIX E: ESTIMATION OF COST USED IN THE COST-EFFECTIVENESS ANALYSIS OF SCREENING AND DIAGNOSTIC STRATEGIES FOR DOWN SYNDROME

APPENDIX E : ESTIMATION OF COSTS USED IN THE COST-EFFECTIVENESS ANALYSIS OF SCREENING AND DIAGNOSTIC STRATEGIES FOR DOWN SYNDROME

Medical visit

A woman's (or couple's) decision to participate in prenatal screening must be based on a clear understanding of what is at stake. Appropriate explanations can be supplied by the physician during a regular or additional prenatal visit. The estimated cost of this visit is $29.30 (Table E.1), the cost of a visit to a general practitioner. We calculated one scenario where the medical visit replaced genetic counselling.

Genetic counselling

Genetic counselling is essential following screening in order to explain to the woman (or couple) the meaning of the result obtained – i.e. whether the risk is high or low. The cost of a genetic counselling visit is estimated at $38.70 (Table E.1) per half-hour. Our base case scenario includes one hour of genetic counselling ($77.40) for all women considered at high risk after screening. This duration was reported as being the average for Canada by the Royal Commission on New Reproductive Technologies [56].

Serum tests

In Quebec, the estimated cost of the serum test varies between $21.16 and $26.16 (Table E.2). However, this could be as high as $60 in someinstances. The cost of a serum test in Ontario, which was initially $86.00, is now $27.50. The approved reimbursement is $35.00, including genetic counselling. The base case scenario used a rate of $26.16. Two scenarios were calculated using $20 and $60, respectively. The $60 maximal cost allows us to include the opinion of professionals in the analysis and takes into account the uncertainty as to the cost of unconjugated estriol testing.

Ultrasonography

The cost of a routine obstetric ultrasound examination is estimated between $25.00 and $28.50 (Table E.3). The estimated cost of diagnostic obstetric ultrasound is $60.00 (Table E.4). The Royal Commission on New Reproductive Technologies estimated the average cost of ultrasound in Ontario and British Columbia to be at least $73.00. However, the report did not differentiate between routine, screening and diagnostic ultrasounds, and the Commission emphasized that the professional fees in these two provinces were high [4]. In order not to minimize the economic impact of ultrasound examinations, the base case scenario uses a cost of $25 (minimum $20; maximum $60), the maximum ($60) being our estimate for diagnostic ultrasonography.

Appendix E: Estimation of Costs Used in the Cost-Effectiveness Analysis of Screening and Diagnostic Strategies for Down Syndrome

Table E.1: Professional fees for various types of medical visits and a 30-minute genetic counselling visit

	Professional fee	Data source (procedure code)
General practitioner	$29.30	RAMQ*
Specialist, main visit Office Outpatient	 $29.50 $22.00	 RAMQ (9149) RAMQ (9175)
Prenatal visit Normal pregnancy High-risk pregnancy	 $12.00 $16.50	 RAMQ September 95 (9164) RAMQ September 95 (9167)
Genetic counselling (half-hour visit)	$38.70	RAMQ April 97 (9056-9059)

* RAMQ: *Régie de l'assurance-maladie du Québec*

Amniocentesis

The estimated total cost of amniocentesis, including ultrasound visualization of the amniotic sac and fetus, collection of amniotic fluid, culture of fetal cells and karyotyping, is $468.28; this also includes professional fees (Table E.5). The Royal Commission on New Reproductive Techniques estimated the average cost of amniocentesis in Canada as varying between $430 in Quebec and $2,020 in Newfoundland, including a consultation session, laboratory costs, the procedure itself and at least one ultrasound billing [56]. In Ontario, the estimated cost under the maternal serum screening program is $500.

Iatrogenic fetal loss and termination of pregnancy

The costs related to termination of pregnancy following amniocentesis are considered to be indirect costs. They have not been included in the analysis and are presented here for information purposes only. The cost of terminating a pregnancy in-hospital is estimated at $970 to $1,190 with curettage (DRG 381) and $1,196 to $1,365 without curettage (DRG 380) (Table E.6).

Private laboratory costs

Table E.7 illustrates the costs of the various procedures in a Quebec laboratory providing prenatal screening and diagnostic services.

Table E.2: Costs related to maternal serum marker tests

	Item		Cost	Total
1	Reagents		$5-10	$5-10
2	Sampling Tube, needle Phlebotomy by nurse (5')	(hourly rate: $30)	 $0.15 $2.50	 $2.75
3	Centrifugation and handling (1-4') Aliquots (2-3') Transportation (2-4') Technician (10')	(hourly rate: $25)	$4.00	$4.00
4	Analysis and results 1 ETP technician/year/10,000 tests	(annual salary: $40,000)	$4.50	$4.50
5	Information brochure Data entry form Pre-analysis data entry by secretary (5')	(hourly rate: $17)	$0.20 $0.20 $1.50	 $1.90
6	Transportation of sample		$0.50	$0.50
7	Sending report to physician Sending report to cytogenetics laboratory		$1.00 $1.00	$2.00
8	Data bank interpretation and management software (rental and update)*	$2,250 per year x 7 laboratories	 $0.51	 $0.51
	Total			$21.16 $26.16

* Data provided by Benetech Co. for AFP Expert software (K. McEvoy, personal communication, July 17/98). This assumes a Windows version software. Reductions can be obtained on purchase of seven sets of software; however, adapting the software to French (for correspondence, reports, brochures) represents additional costs. The maximal cost supplied by the company is used in this analysis.

Table E.3 : Costs related to ultrasonography for estimation of week of gestation

	Estimated cost	Source (procedure code)
Professional fees Ultrasound at < 16 wks Ultrasound at 16 wks and +	 $15.00 $18.50	 RAMQ MD specialists, September 95 (8315) RAMQ MD specialists, September 95 (8317)
Other costs (material, equipment, photo, forms, reports)	$10.00	Items 5 and 7 of Table E.2, plus printing image for mother and medical records, plus material and equipment
Total	$25.00 to $28.50	

Note: The Royal Commission on New Reproductive Technologies estimated the cost of ultrasound in Ontario and British Columbia at $73.00 for 1989-1990. A difference in professional fees may partially account for the difference with the cost estimated for Quebec. In addition, it was impossible to separate out routine and diagnostic ultrasounds. The cost of diagnostic ultrasound in Quebec has been estimated at $50.00. In a number of centres, the ultrasound examination is carried out by a technician. We have not included the 15-minute cost for the technician (about $8.50).

Table E.4: Costs related to diagnostic ultrasonography

	Estimated cost	Source (procedure code)
Cost of ultrasound	$22.50	See note 1
Professional fees	$18.50	RAMQ MD specialists, September 95 (8317)
Technician	$8.50	See note 2
Other costs (material, equipment, photo, forms, reports)	$10.00	Items 5 and 7 of Table E.2, plus printing of image for mother and medical record, plus material and equipment
Total	$60.00	

Note 1: The equipment cost is estimated at $250,000, depreciated over two years. The machine operates 1,400 hours/year, at a cost of $90/hour. An ultrasound test takes 15' on average; the cost per ultrasound is thus $22.50.

Note 2: The technician's salary is estimated at $47,000/year, or $33.00/hour. The cost per ultrasound is estimated as $8.50.

Table E.5: Costs related to amniocentesis and karyotyping

	Estimated cost	Source
Professional fees Amniocentesis Culture and karyotyping	 $27.60 $50.68	 RAMQ MD general practitioners, April 97 (6927) RAMQ MD specialists, Sept. 96 (+54010)
Culture and karyotype	$350.00	Measures of Production
Other (at least one ultrasound billed, transportation of sample, etc.)	$40.00	Based on cost estimates made by the Royal Commission
Total	$468.28	See note

Note 1: The Royal Commission on New Reproductive Technologies [56] estimated the cost of amniocentesis in Quebec as $430, including $37 for a consultation session. We calculated the cost of genetic counselling separately.

Table E.6: Costs related to termination of pregnancy

	Hospitalization Cost	Day surgery cost	Source
With curettage or hysterectomy (DRG381): Professional fees Hospitalization, 1.3 days average stay Day surgery, 1 day	 $90 $130 (office) $1060	 $90 $130 (office) $880	 RAMQ [1] MSSS [2]
Total	$1150 - $1190	$970 - $1010	
Without curettage (DRG380): Professional fees Hospitalization, 1.7 days average stay Day surgery, 1 day	 $200 $250 $ (office) $1115	 $200 $250 (office) $996	 RAMQ [3] MSSS [2]
Total	$1315 - $1365	$1196 - $1246	

[1] Codes 6906 and 6939 according to RAMQ MAJ 37/April 97

[2] MSSS data for the year 95-96 and personal communication by J. Paquin, MSSS research officer, February 18, 1998 [87]
No. of DRG381 cases: 2,435 cases x 1.3 days hospitalization, and 1,694 cases x 1 day hospitalization
No. of DRG380 cases: 385 cases x 1.7 days hospitalization, and 84 cases x 1 day hospitalization

[3] Codes 6941 and 6947 according to RAMQ MAJ 37/April 97

Table E.7: Costs of various procedures in private laboratories in Quebec

Procedure	Cost
Triple marker test (ßhCG, AFP, Estriol)	$150
Obstetric ultrasound	$90
Amniocentesis, culture and karyotype	$675[1]

[1] The cost for prenatal cytogenetics (test only) is $500
Information obtained from PROCREA website (URL: http://www.procrea.qc.ca/lab/labset.html)

APPENDIX F:
SENSITIVITY ANALYSIS – TABLES OF RESULTS

SENSITIVITY ANALYSIS – TABLES OF RESULTS

SENSITIVITY ANALYSIS VARYING THE EFFECTIVENESS PARAMETERS

Table F.1: Approach #2: Universal MSS

	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	Total cost ($)	Variation (%)*
Base case scenario	**34**	**14**	**82**	**2,753,210**	
Scenario A: Maximum detection rate	36	18	89	3,166,879	**+ 15**
Scenario B: Minimum detection rate	31	11	76	2,338,752	**- 15**
Scenario C: Maximum participation rate	39	16	79	3,088,948	**+ 12**
Scenario D: Minimum participation rate	29	12	84	2,431,713	**- 12**
Scenario E: 1% iatrogenic fetal loss	34	28	82	2,753,210	**0**

* Variation between total cost of scenario specified and total cost of base case scenario

Table F.2: Approach #3: Universal MSS, Amnio 35 +

	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	Total cost ($)	Variation (%)*
Base case scenario	**51**	**32**	**91**	**4,651,751**	
Scenario A: Maximum detection rate	53	35	95	5,065,416	**+ 9**
Scenario B: Minimum detection rate	48	28	88	4,237,293	**- 9**
Scenario C: Maximum participation rate	56	33	88	4,875,809	**+ 5**
Scenario D: Minimum participation rate	47	30	93	4,417,115	**- 5**
Scenario E: 1% iatrogenic fetal loss	51	63	91	4,651,751	**0**

* Variation between total cost of scenario specified and total cost of base case scenario

Table F.3: Approach #4: MSS < 35, Amnio 35 +

	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	Total cost ($)	Variation (%)*
Base case scenario	**59**	**51**	**113**	**6,631,616**	
Scenario A: Maximum detection rate	60	54	116	6,994,879	+ 5
Scenario B: Minimum detection rate	57	48	110	6,267,890	- 5
Scenario C: Maximum participation rate	64	55	112	7,173,864	+ 8
Scenario D: Minimum participation rate	54	47	113	6,101,824	- 8
Scenario E: 1% iatrogenic fetal loss	59	102	113	6,631,616	0

* Variation between total cost of scenario specified and total cost of base case scenario

Table F.4: Approach #5: Universal MSS, Amnio 37 +

	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	Total cost ($)	Variation (%)*
Base case scenario	**46**	**23**	**80**	**3,693,088**	
Scenario A: Maximum detection rate	48	26	85	4,106,753	+ 11
Scenario B: Minimum detection rate	43	19	76	3,278,630	- 11
Scenario C: Maximum participation rate	51	25	78	3,973,538	+ 8
Scenario D: Minimum participation rate	42	21	81	3,414,592	- 8
Scenario E: 1% iatrogenic fetal loss	46	46	80	3,693,088	0

* Variation between total cost of scenario specified and total cost of base case scenario

Table F.5: Approach #6: MSS < 37, Amnio 37 +

	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	Total cost ($)	Variation (%)*
Base case scenario	**52**	**32**	**90**	**4,671,139**	
Scenario A: Maximum detection rate	53	36	95	5,059,780	+ 8
Scenario B: Minimum detection rate	50	29	86	4,281,943	- 8
Scenario C: Maximum participation rate	57	36	89	5,108,815	+ 9
Scenario D: Minimum participation rate	47	29	91	4,246,804	- 9
Scenario E: 1% iatrogenic iatrogenic fetal loss	52	65	90	4,671,139	0

* Variation between total cost of scenario specified and total cost of base case scenario

Table F.6: Scenarios representing the best and worst estimates for all effectiveness parameters

	Best scenario			Worst scenario		
	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)	DS cases diagnosed (no.)	Iatrogenic fetal loss (no.)	Cost/case diagnosed ($000)
Amnio 35 +	**28**	**27**	**98**	**28**	**27**	**98**
Approach #2	41	20	86	26	9	79
Approach #3	58	37	92	45	27	91
Approach #4	66	59	116	52	44	111
Approach #5	53	29	84	39	18	78
Approach #6	59	39	94	45	27	87

SENSITIVITY ANALYSIS VARYING COSTS

Table F.7: Variation in genetic counselling costs for each approach and with base case scenario effectiveness parameters

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Genetic counselling (1½ hrs)					
Total cost/year	$2,882,670	$4,915,857	$7,044,072	$3,889,205	$4,940,537
C/E ratio	$85,555	$95,704	$119,544	$83,895	$95,422
Variation from base case scenario	**+ 5%**	**+ 6%**	**+ 6%**	**+ 5%**	**+ 6%**
Genetic counselling (30 min)					
Total cost/year	$2,623,750	$4,387,644	$6,219,159	$3,496,971	$4,401,742
C/E ratio	$77,871	$85,421	$105,544	$75,434	$85,015
Variation from base case scenario	**- 5%**	**- 6%**	**- 6%**	**- 5%**	**- 6%**
MD visit instead of genetic counselling					
Total cost/year	$2,592,304	$4,323,495	$6,118,976	$3,449,335	$4,336,307
C/E ratio	$76,937	$84,172	$103,844	$74,406	$83,752
Variation from base case scenario	**- 6%**	**- 7%**	**- 8%**	**- 7%**	**- 7%**

Table F.8: Variation in MSS costs for each approach and with base case scenario effectiveness parameters

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Maximum cost of MSS					
Total cost/year	$4,149,147	$6,047,688	$7,858,258	$5,089,025	$5,983,267
C/E ratio	$123,143	$117,739	$133,361	$109,776	$115,561
Variation from base case scenario	**+ 51%**	**+ 30%**	**+ 18%**	**+ 38%**	**+ 28%**
Minimum cost of MSS					
Total cost/year	$2,499,103	$4,397,644	$6,408,326	$3,438,981	$4,432,289
C/E ratio	$74,171	$85,615	$108,755	$74,183	$85,605
Variation from base case scenario	**- 9%**	**- 5%**	**- 3%**	**- 7%**	**- 5%**

Table F.9: Variation in ultrasound costs for each approach and with base case scenario effectiveness parameters

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Maximum ultra-sound cost					
Total cost/year	$2,870,293	$4,768,834	$6,734,033	$3,810,171	$4,780,816
C/E ratio	$85,188	$92,842	$114,282	$82,190	$92,337
Variation from base case scenario	**+ 4%**	**+ 3%**	**+ 2%**	**+ 3%**	**+ 2%**
Minimum ultrasound cost					
Total cost/year	$2,736,484	$4,635,025	$6,616,985	$3,676,362	$4,655,471
C/E ratio	$81,217	$90,237	$112,296	$79,303	$89,916
Variation from base case scenario	**- 1%**	**- 0.4%**	**- 0.2%**	**- 0.5%**	**- 0.3%**

Table F.10: Variation in amniocentesis costs for each approach and with base case scenario effectiveness parameters

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Maximum cost for amniocentesis					
Total cost/year	$2,888,708	$4,852,306	$6,955,758	$3,837,916	$4,877,038
C/E ratio	$84,390	$94,467	$118,045	$82,788	$94,195
Variation from base case scenario	**+ 3%**	**+ 4%**	**+ 5%**	**+ 4%**	**+ 4%**
Minimum cost for amniocentesis					
Total cost/year	$2,559,059	$4,220,039	$5,933,871	$3,381,332	$4,227,925
C/E ratio	$75,951	$82,158	$100,703	$72,939	$81,658
Variation from base case scenario	**- 7%**	**- 9%**	**- 11%**	**- 8%**	**- 9%**

Table F.11: Highest and lowest costs for each intervention and with base case scenario effectiveness parameters

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Highest cost					
Total cost/year	$4,485,885	$6,629,432	$8,697,274	$5,547,054	$6,568,239
C/E ratio	$133,137	$129,065	$147,600	$119,656	$126,859
Variation from base case scenario	**+ 63%**	**+ 43%**	**+ 31%**	**+ 50%**	**+ 41%**
Lowest cost					
Total cost/year	$2,127,321	$3,620,950	$5,183,311	$2,866,746	$3,638,574
C/E ratio	$63,137	$70,494	$87,965	$61,839	$70,275
Variation from base case scenario	**- 23%**	**- 22%**	**- 22%**	**- 22%**	**- 22%**

Table F.12: Scenario results assuming an ultrasound performed before screening

	2 Universal MSS	3 Universal MSS Amnio 35 +	4 MSS < 35 Amnio 35 +	5 Universal MSS Amnio 37 +	6 MSS < 37 Amnio 37 +
Base case scenario					
Cases diagnosed	34	51	59	46	52
Iatrogenic fetal loss	14	32	51	23	32
Total cost/year	**$2,753,210**	**$4,651,751**	**$6,631,616**	**$3,693,088**	**$4,671,139**
C/E ratio	**$81,713**	**$90,562**	**$112,544**	**$79,664**	**$90,128**
Ultrasound before screening					
Cases diagnosed	35	52	60	47	53
Iatrogenic fetal loss	9	26	46	18	28
Total cost/year	**$3,114,369**	**$5,012,910**	**$6,948,752**	**$4,054,247**	**$5,010,435**
C/E ratio	**$89,673**	**$95,663**	**$116,728**	**$85,542**	**$95,431**

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